(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 January 2003 (03.01.2003)

PCT

(10) International Publication Number
WO 03/000670 A1

(51) International Patent Classification[7]: C07D 267/20, 281/16, A61K 31/553, 31/554, A61P 25/18

(21) International Application Number: PCT/CA02/00956

(22) International Filing Date: 26 June 2002 (26.06.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/300,430 26 June 2001 (26.06.2001) US

(71) Applicant *(for all designated States except US)*: **NEUROMOLECULAR, INC.** [CA/CA]; 105 Adelaide Street West, Toronto, Ontario M5H 1P9 (CA).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **KAPUR, Shitij** [CA/CA]; 334 Carlton Street, Toronto, Ontario M5A 2M1 (CA). **MCCLELLAND, Robert** [CA/CA]; 8 Wetherfield Place, Don Mills, Ontario M3B 2E1 (CA).

(74) Agent: **LEDGLEY, Cynthia, J.**; 121 Richmond Street West, Suite 1000, Toronto, Ontario M5H 2K1 (CA).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

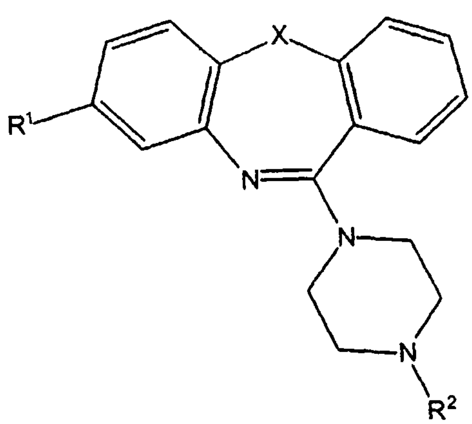
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: A11-PIPERAZINYLDIBENZO (B, F) (1, 4) OXAZEPINES AND THIAZEPINES AS ATYPICAL ANTIPSYCHOTIC AGENTS HAVING LOW AFFINITY FOR THE D2 RECEPTOR



(I)

(57) Abstract: The present invention provides novel compounds of Formula (I). The invention further relates to pharmaceutical compositions comprising compounds of Formula I and to methods of using compounds of Formula I to treat neuropsychiatric disorders (e.g., psychosis, depression, schizophrenia).

WO 03/000670 A1

A11-PIPERAZINYLDIBENZO (B,F)(1,4) OXAZEPINES AND THIAZEPINES AS ATYPICAL ANTIPSY CHOTIC AGENTS HAVING LOW AFFINITY FOR THE D2 RECEPTOR

CROSS-REFERENCE TO RELATED APPLICATION

This application claims priority to U.S. Provisional Patent Application Serial No. 60/300,430, filed June 26, 2001, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

This invention relates to novel compounds and their use as antipsychotics. In particular, the invention relates to compounds having atypical dopamine receptor affinity, methods of preparing such compounds and to their use for therapeutic and drug screening purposes.

BACKGROUND OF THE INVENTION

There are currently several antipsychotics available for regular clinical use. Every one of them blocks dopamine D_2 receptors (Seeman and Tallerico 1998). See Index of Articles cited herein. This includes the older "typical" as well as the newer "atypical" antipsychotics. "Atypical" antipsychotic is a term that is used to define antipsychotics which have a lower or minimal incidence of side effects. With the exception of a few dopamine-depleting agents, there is no receptor-drug profile other than D_2 receptor blockage that is able to achieve antipsychotic activity. However, a central problem in the use of antipsychotics is that of related side effects. The two major side effects of concern have been extrapyramidal side effects ("EPS") as well as prolactin elevation. Side effects limit the number of patients who agree to take these medications, as they tend to decrease compliance and high levels of EPS may actually decrease the efficacy of the medications.

Without being bound by theory, it is believed that EPS and prolactin elevation also result from dopamine D_2 blockade. In particular, the blockade of D_2 receptors in the tubero-infundibular system is thought to be responsible for prolactin elevation (Moore 1987), while the blockade of the dopamine D_2 receptors in the striatum is thought to be responsible for EPS (Farde et al. 1997). A corollary of prolonged blockade of the dopamine D_2 system is thought to be tardive dyskinesia which occurs

after several years of use of antipsychotics that cause EPS (Casey 1996). Thus, avoiding these side effects is a central way of improving antipsychotics.

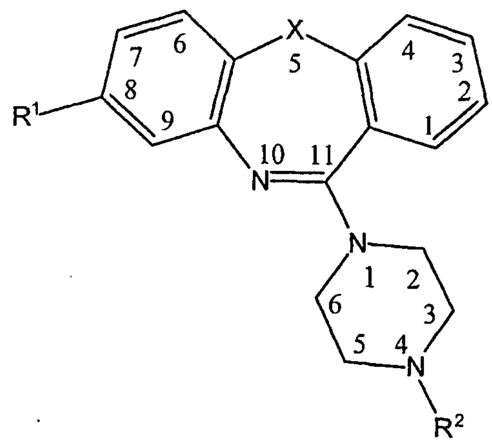
The current gold-standard for an atypical antipsychotic is clozapine. However, in some patients clozapine has the serious shortcoming of blood dyscrasias, or agranulocytosis, which means that all patients on this medication must have their blood tested regularly. This side-effect is the Achille's heel of clozapine. It has limited the use of this most effective antipsychotic (in terms of efficacy and "atypicality") to being the drug of last resort because of this ongoing need for regular blood testing of each patient on the medication.

There is therefore a need for new effective antipsychotic drugs exhibiting minimal side effects (e.g., diminished or absent EPS, prolactin elevation and/or agranulocytosis side effects).

SUMMARY OF THE INVENTION

Novel tricyclic piperazine compounds have been prepared and found to have a high K_i (Note: $K_i = K_{off}/K_{on}$) for the dopamine D_2 receptor of at least 30nM, preferably above about 40 nM, and/or a K_{off} sufficiently large to enable interaction between the dopamine D_2 receptor and the novel compound(s) to yield their beneficial "atypical" antipsychotic efficacy i.e., with greatly diminished or without the side effects associated with the "typical" antipsychotics. These compounds have been shown to act as atypical antipsychotics in animal behavior assays.

The present invention therefore provides compounds of Formula I:



I

wherein:

R^1 is selected from the group consisting of halo, CF_3, CF_3O, cyano, CH_3 and CH_3O;

R^2 is selected from the group consisting of $C_{2\text{-}5}$alkyl and $(CH_2)_nOH$;

X is selected from the group consisting of O and S;

n is 2-5; and

pharmaceutically acceptable salts, hydrates, prodrugs and solvates thereof.

According to other embodiments of the present invention, the above compounds of Formula I have a K_i value (affinity for the dopamine D_2 receptor) as noted below in items (1) to (12). Also, the below-noted K_i values are measured according to the procedures described in Seeman 1993 (cited herein) using raclopride as the standard ligand:

(1) K_i value for the dopamine D_2 receptor of at least 30nM (nanomoles);

(2) K_i value for the dopamine D_2 receptor from 30nM to about 500nM;

(3) K_i value for the dopamine D_2 receptor of at least about 40nM;

(4) K_i value for the dopamine D_2 receptor from about 40nM to about 500nM;

(5) K_i value for the dopamine D_2 receptor from about 40nM to about 250nM;

(6) K_i value for the dopamine D_2 receptor from about 40nM to about 180nM;

(7) K_i value for the dopamine D_2 receptor from about 40nM to about 120nM;

(8) K_i value for the dopamine D_2 receptor from about 40nM to about 80nM;

(9) K_i value for the dopamine D_2 receptor of at least about ½ x (K_i for clozapine);

(10) K_i value for the dopamine D_2 receptor from about ½ x (K_i for clozapine) to about 6½ x (K_i for clozapine);

(11) K_i value for the dopamine D_2 receptor from about ½ x (K_i for clozapine) to about 4 x (K_i for clozapine); and

(12) K_i value for the dopamine D_2 receptor from about ½ x (K_i for clozapine) to about 2 x (K_i for clozapine).

The present invention also provides compounds of Formula I wherein R^1 is selected from the group consisting of halo and CF_3 and wherein R^2, X and n are as defined in Formula I.

The present invention also provides compounds of Formula I wherein R^1 is selected from the group consisting of F, Cl and CF_3, and wherein R^2, X and n are as defined in Formula I.

Further, the present invention provides compounds of Formula I wherein R^1 is Cl and wherein R^2, X and n are as defined in Formula I.

There are also provided compounds of Formula I wherein R^2 is selected from the group consisting of C_{2-4} alkyl and $(CH_2)_nOH$ and wherein R^1, X and n are as defined in Formula I. Further, the present invention provides compounds of Formula I wherein R^2 is selected from the group consisting of ethyl, n-propyl, isopropyl, butyl

and $(CH_2)_2OH$ and wherein R^1 and X are as defined in Formula I. The present invention further provides compounds of Formula I wherein R^2 is selected from the group consisting of ethyl and $(CH_2)_2OH$ and wherein R^1 and X are as defined in Formula I.

There are also provided compounds of Formula I wherein X is O and wherein R^2, R^1 and n are as defined in Formula I.

The invention further relates to pharmaceutical compositions comprising a compound of Formula I and a pharmaceutically acceptable carrier and/or diluent.

According to another broad aspect of the present invention, there is provided a method of treating neuropsychiatric disorders (including, but not limited to, conditions associated with or leading to psychosis, emotional and behavioral disturbances, schizophrenia and schizophrenia spectrum disorders, psychotic disorders in the context of affective disorders, depression, psychosis disorders induced by drugs/medication (such as Parkinson's psychosis), drug induced movement disorders (dyskinesias in Parkinson's disease), psychosis and behavioral disorders in the context of dementias and psychotic disorders due to a general medical conditions, or combinations thereof) comprising administering to a patient or subject (e.g., a human or an animal such as a dog) in need thereof a therapeutically effectively amount of a compound of Formula I. Preferably, the compound of Formula I is combined with a pharmaceutically acceptable carrier and/or diluent.

Other features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples while indicating preferred embodiments of the invention are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

DETAILED DESCRIPTION OF THE INVENTION

1. Definitions

The term "halo" as used herein means halogen and includes chloro, fluoro, bromo, and iodo.

The term "C_{2-5}alkyl" as used herein means straight and branched chain alkyl radicals containing from two to five carbon atoms and includes ethyl, propyl, isopropyl, n-butyl, t-butyl, n-pentyl and the like.

The term "compound(s) of the invention" as used herein means a compound of Formula I and salts, hydrates, prodrugs and solvates thereof.

The term "pharmaceutically acceptable salt" means an acid addition salt which is suitable for or compatible with the treatment of a patient or a subject such as a human patient or an animal such as a dog.

The term "pharmaceutically acceptable acid addition salt" as used herein means any non-toxic organic or inorganic salt of any base compounds represented by Formula I or any of their intermediates. Illustrative inorganic acids which form suitable acid addition salts include hydrochloric, hydrobromic, sulfuric and phosphoric acids, as well as metal salts such as sodium monohydrogen orthophosphate and potassium hydrogen sulfate. Illustrative organic acids that form suitable acid addition salts include mono-, di-, and tricarboxylic acids such as glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, benzoic, phenylacetic, cinnamic and salicylic acids, as well as sulfonic acids such as p-toluene sulfonic and methanesulfonic acids. Either the mono or di-acid salts can be formed, and such salts may exist in either a hydrated, solvated or substantially anhydrous form. In general, the acid addition salts of compounds of Formula I are more soluble in water and various hydrophilic organic solvents, and generally demonstrate higher melting points in comparison to their free base forms. The selection of the appropriate salt will be known to one skilled in the art. Other non-pharmaceutically acceptable salts, e.g. oxalates, may be used, for example, in the

isolation of compounds of Formula I for laboratory use, or for subsequent conversion to a pharmaceutically acceptable acid addition salt.

The term "solvate" as used herein means a compound of Formula I, or a pharmaceutically acceptable salt of a compound of Formula I, wherein molecules of a suitable solvent are incorporated in the crystal lattice. A suitable solvent is physiologically tolerable at the dosage administered. Examples of suitable solvents are ethanol, water and the like. When water is the solvent, the molecule is referred to as a "hydrate."

The term an "effective amount" or a "sufficient amount " of an agent as used herein is that amount sufficient to effect beneficial or desired results, including clinical results, and, as such, an "effective amount" depends upon the context in which it is being applied. For example, in the context of administering an agent that acts as an atypical antipsychotic, an effective amount of an agent is, for example, an amount sufficient to achieve such a reduction in psychoses, without unwanted side effects such as, for example EPS and prolactin elevation, as compared to the response obtained without administration of the agent. The term "effective amount" also includes that amount of the compound of Formula I which is "therapeutically effective" and which avoids or substantially attenuates undesirable side effects such as EPS, prolactin elevation and /or blood dyscrasias.

As used herein, and as well understood in the art, "treatment" is an approach for obtaining beneficial or desired results, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of extent of disease, stabilized (i.e. not worsening) state of disease, preventing spread of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment.

"Palliating" a disease or disorder means that the extent and/or undesirable clinical manifestations of a disorder or a disease state are lessened and/or time course of the progression is slowed or lengthened, as compared to not treating the disorder.

To "diminish" or "inhibit" or "suppress" or "reduce" a function or activity, such as psychoses, is to reduce the function or activity when compared to otherwise same conditions except for a condition or parameter of interest, or alternatively, as compared to another condition.

The terms "animal," "subject" and "patient" as used herein include all members of the animal kingdom including, but not limited to, mammals, animals (e.g. cats, dogs, horses, etc.) and humans. The animal is preferably a human.

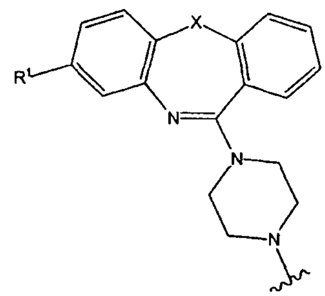
As used herein "low binding affinity" means a relatively high K_i, of at least 30nM (or at least about 40nM), or of at least about ½ x (K_i for clozapine) sufficient to yield the beneficial antipsychotic effects associated with "atypical" antipsychotics with reduced or diminished or altogether without the detrimental side effects of "typical" antipsychotics such as EPS etc. described above. The "low binding affinity" may be one that falls within ranges of items (1) to (12) noted above measured using raclopride as the standard ligand. As will be appreciated by those skilled in the art, K_i values depend on the method of measurement, pH, radiolabeling technique, tissue type, temperature and type of wash used. The greatest differences depend upon the ligand standard used, for example with clozapine, a K_i of 76 nM is obtained with raclopride as the standard, but a K_i of 180 nM is obtained when spiperone is used as the standard, even under identical conditions. Accordingly, K_i and "low binding affinity" as used herein encompass this understanding and the K_i values recited herein are based on K_i values measured using raclopride as the standard according to the procedure outlined in Seeman 1993. Preferably, a control K_i measurement should be made simultaneously, for example, with clozapine to standardize the K_i value measured to offset any effects of variations in the measuring conditions such as pH, temperature, tissue type etc. noted above.

As used herein a "fast off-rate" means a relatively high K_{off}, on the order of approximately 0.6 min^{-1} or greater sufficient to yield the beneficial antipsychotic effects associated with "atypical" antipsychotics with reduced or diminished or altogether without the detrimental side effects of "typical" antipsychotics such as EPS etc. described above. The same consideration in respect of K_i and low binding affinity also apply to K_{off} and "fast off-rate". Thus, the "fast off-rate" may be one that falls within ranges of items (1) –(12) noted above using clozapine as the standard. See Kapur and Seaman 2000a.

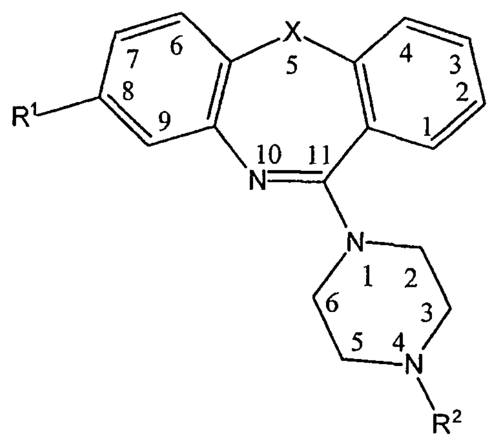
2. Preferred Compounds of the Invention

As hereinbefore described, it is expected that atypical antipsychotic activity may be achieved with a drug that blocks the dopamine D_2 receptor with a high K_i, preferably of at least 30 nM, and/or a fast off-rate (K_{off}), preferably greater than about 0.6 min^{-1} sufficient to yield the beneficial antipsychotic effects associated with "atypical" antipsychotics with reduced or diminished or altogether without the detrimental side effects of "typical" antipsychotics such as EPS etc. described above. Exemplary K_{off} values suitable for use with the present invention include, but are not limited to, from about 0.6 min^{-1} to about 10.0 min^{-1}, from about 0.8 min^{-1} to about 10.0 min^{-1}, from about 0.9 min^{-1} to about 9.0 min^{-1}, from about 1.0 min^{-1} to about 8.0 min^{-1}, from about 1.1 min^{-1} to about 7.0 min^{-1}, from about 1.2 min^{-1} to about 6.0 min^{-1}, from about 1.5 min^{-1} to about 5.0 min^{-1}, and from about 1.8 min^{-1} to about 3.2 min^{-1}. The measurement for K_{off} may be made according to the procedure outlined in Kapur and Seeman 2000a.

As noted above, according to one embodiment, the invention relates to novel compounds that have a K_i for the D_2 receptor of at least 30 nM and/or a K_{off} greater than about 0.6 min^{-1}. It has been found, more particularly, that D_2-binding ligands having the tricyclic structure:



have a K_i of at least 30 nM and/or a K_{off} of at least about 0.6 min^{-1} (sufficient to yield the beneficial antipsychotic effects associated with "atypical" antipsychotics with reduced or diminished or altogether without the detrimental side effects of "typical" antipsychotics such as EPS etc. described above), and therefore are effective as atypical antipsychotics, when the piperazine group is derivatized by a group designated R^2 as noted below. In accordance with one of its aspects, the present invention therefore provides compounds of Formula I:



I

wherein

R^1 is selected from the group consisting of halo, CF_3, CF_3O, cyano, CH_3 and CH_3O;

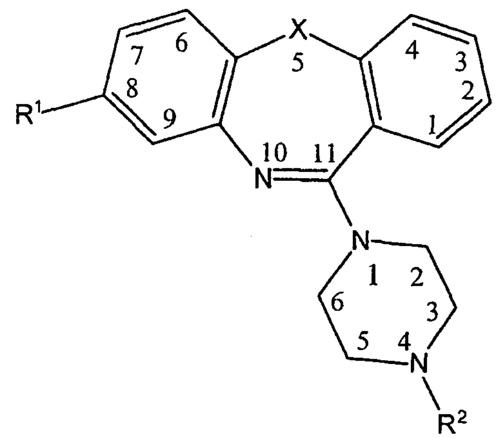
R^2 is selected from the group consisting of C_{2-5}alkyl and $(CH_2)_nOH$;

X is selected from the group consisting of O and S;

n is 2-5; and

pharmaceutically acceptable salts, hydrates, prodrugs and solvates thereof.

In accordance with one of its embodiments, the present invention therefore provides compounds of Formula I:



I

wherein:

R^1 is selected from the group consisting of halo, CF_3, CF_3O, cyano, CH_3 and CH_3O;

R^2 is selected from the group consisting of C_{2-5}alkyl and $(CH_2)_nOH$;

X is selected from the group consisting of O and S;

n is 2-5; and

a pharmaceutically acceptable salt, hydrate, prodrug or solvate thereof; and wherein:

said compound of Formula I has a K_i for the dopamine D_2 receptor in any one of the value ranges noted in items (1) to (12) as follows:

(1) K_i value for the dopamine D_2 receptor of at least 30nM (nanomoles);

(2) K_i value for the dopamine D_2 receptor from 30nM to about 500nM;

(3) K_i value for the dopamine D_2 receptor of at least about 40nM;

(4) K_i value or the dopamine D_2 receptor from about 40nM to about 500nM;

(5) K_i value for the dopamine D_2 receptor from about 40nM to about 250nM;

(6) K_i value for the dopamine D_2 receptor from about 40nM to about 180nM;

(7) K_i value for the dopamine D_2 receptor from about 40nM to about 120nM;

(8) K_i value for the dopamine D_2 receptor from about 40nM to about 80nM;

(9) K_i value for the dopamine D_2 receptor of at least about ½ x (K_i for clozapine);

(10) K_i value for the dopamine D_2 receptor from about ½ x (K_i for clozapine) to about 6½ x (K_i for clozapine);

(11) K_i value for the dopamine D_2 receptor from about ½ x (K_i for clozapine) to about 4 x (K_i for clozapine); and

(12) K_i value for the dopamine D_2 receptor from about ½ x (K_i for clozapine) to about 2 x (K_i for clozapine).

As previously noted, the above-noted K_i values are measured according to the procedure described in Seeman 1993 (cited herein) using raclopride as the standard ligand.

In embodiments of the invention, compounds of Formula I are those in which R^1 is selected from the group consisting of halo, CF_3, CF_3O, cyano, CH_3 and CH_3O. Preferably, R^1 is selected from the group consisting of halo and CF_3. In more preferred embodiments, R^1 is selected from the group consisting of F, Cl and CF_3. In the most preferred embodiment, R^1 is Cl.

Further embodiments of the invention include compounds of Formula I wherein R^2 is selected from the group consisting of C_{2-5}alkyl and $(CH_2)_nOH$, where n is 2, 3, 4 or 5. Preferred embodiments include compounds of Formula I where R^2 is selected from the group consisting of C_{2-4} alkyl and $(CH_2)_nOH$ and n is 2-3. More preferably, R^2 is selected from the group consisting of ethyl, n-propyl, isopropyl,

butyl and $(CH_2)_2OH$. Most preferred are compounds of Formula I wherein R^2 is selected from the group consisting of ethyl and $(CH_2)_2OH$.

Compounds of Formula I further include those in which X is selected from O and S. The oxazepines and thiazepines are expected to have a reduced propensity for the hematological side-effect, agranulocytosis (Uetrecht et al. 1997). This particular side effect is responsible for the limited clinical use of clozapine. Preferred are compounds of Formula I where X is O.

In specific embodiments of the invention, the compounds of Formula I include:

(A-1) 8-Trifluoromethyl-11-(4-ethylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-2) 8-Trifluoromethyl-11-(4-(2'-hydroxyethyl)piperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-3) 8-Trifluoromethyl-11-(4-propylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-3a) 8-Trifluoromethyl-11-(4-propylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine•HCl;

(A-4) 8-Trifluoromethyl-11-(4-isopropylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-4a) 8-Trifluoromethyl-11-(4-isopropylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine•HCl;

(A-5) 8-Trifluoromethyl-11-(4-butylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-5a) 8-Trifluoromethyl-11-(4-butylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine•HCl;

(A-6) 8-Chloro-11-(4-ethylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-6a) 8-Chloro-11-(4-ethylpiperazin-1-yl)-dibenzo [b,f][1,4]oxazepine•HCl;

(A-7) 8-Chloro-11-(4-(2'-hydroxyethyl)piperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-8) 8-Chloro-11-(4-propylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-9) 8-Chloro-11-(4-isopropylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-10) 8-Chloro-11-(4-butylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-11) 8-Fluoro-11-(4-ethylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-12) 8-Chloro-11-(4-ethylpiperazin-1-yl)-dibenzo [b,f][1,4]thiazepine;

(A-13) 8-Chloro-11-(4-(2'-hydroxyethyl)piperazin-1-yl)-dibenzo[b,f][1,4]thiazepine;

(A-14) 8-Chloro-11-(4-propylpiperazin-1-yl)-dibenzo[b,f][1,4]thiazepine;

(A-14a) 8-Chloro-11-(4-propylpiperazin-1-yl)-dibenzo[b,f][1,4]thiazepine•HCl;

(A-15) 8-Chloro-11-(4-isopropylpiperazin-1-yl)-dibenzo[b,f][1,4]thiazepine;

(A-15a) 8-Chloro-11-(4-isopropylpiperazin-1-yl)-dibenzo[b,f][1,4]thiazepine•HCl;

(A-16) 8-Chloro-11-(4-butylpiperazin-1-yl)-dibenzo[b.f][1,4]thiazepine; and

(A-16a) 8-Chloro-11-(4-butylpiperazin-1-yl)-dibenzo[b.f][1,4]thiazepine•HCl.

More specifically the compounds of Formula I include:

(A-1) 8-Trifluoromethyl-11-(4-ethylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-2) 8-Trifluoromethyl-11-(4-(2'-hydroxyethyl)piperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-6) 8-Chloro-11-(4-ethylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-6a) 8-Chloro-11-(4-ethylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine•HCl;

(A-7) 8-Chloro-11-(4-(2'-hydroxyethyl)piperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-11) 8-Fluoro-11-(4-ethylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-12) 8-Chloro-11-(4-ethylpiperazin-1-yl)-dibenzo [b,f][1,4]thiazepine; and

(A-13) 8-Chloro-11-(4-(2'-hydroxyethyl)piperazin-1-yl)-dibenzo[b,f][1,4]thiazepine.

Even more specifically, the compounds of Formula I include:

(A-6) 8-Chloro-11-(4-ethylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-6a) 8-Chloro-11-(4-ethylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine•HCl;

(A-7) 8-Chloro-11-(4-(2'-hydroxyethyl)piperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-12) 8-Chloro-11-(4-ethylpiperazin-1-yl)-dibenzo [b,f][1,4]thiazepine; and

(A-13) 8-Chloro-11-(4-(2'-hydroxyethyl)piperazin-1-yl)-dibenzo[b,f][1,4]thiazepine.

Most specifically, the compounds of Formula I include:

(A-6) 8-Chloro-11-(4-ethylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

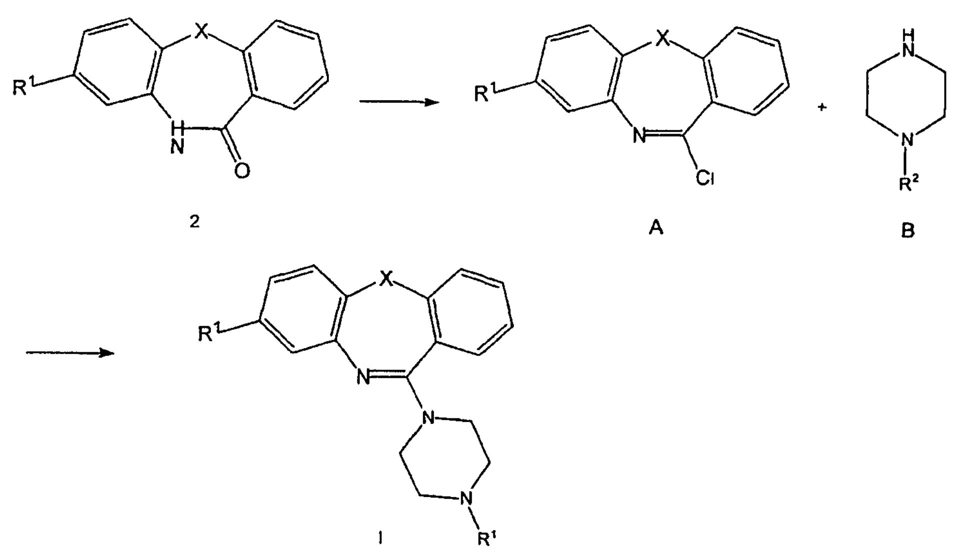
(A-6a) 8-Chloro-11-(4-ethylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine•HCl; and

(A-7) 8-Chloro-11-(4-(2'-hydroxyethyl)piperazin-1-yl)-dibenzo[b,f][1,4]oxazepine.

3. Methods of Preparing Compounds of Formula I

Compounds of Formula I may be prepared using processes analogous to those known in the art. The present invention therefore provides, in a further aspect, a process for the preparation of a compound of Formula I, or a salt, solvate or hydrate thereof, which comprises the step of coupling a reagent of Formula A with a reagent of Formula B, as shown in Scheme 1, wherein R^1 and R^2 and X are as defined in Formula 1. Reagents of Formula A may be prepared from the corresponding lactams 2 by, for example, reaction with phosphorus oxychloride in an inert solvent, such as toluene, in the presence of an organic base, such as a tertiary amine, preferably at refluxing temperatures. Reagents A need not be isolated, but instead may be reacted directly with reagents of Formula B in an inert solvent such as toluene, preferably at refluxing temperatures. Alternatively, Reagents of Formula 2 may be reacted with a reagent of Formula B in the presence of a Lewis Acid such as $TiCl_4$ or BF_3Et_2O to provide compounds of Formula I.

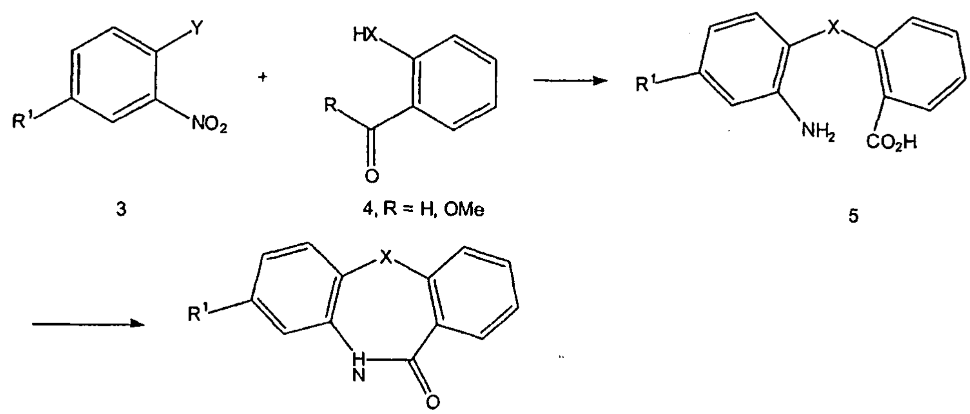
Scheme 1



Lactams 2, where X = O, may be prepared according to the procedures described in Klunder (J. Med. Chem. 1992, 35:1887). Alternatively, lactams 2,

where X is O or S, may be prepared as shown in Scheme 2. Appropriately 4-substituted nitrobenzenes 3, wherein Y is a suitable leaving group such as halo, preferably fluoro or chloro, may be condensed with either aldehyde or esters 4, wherein X is O or S, using, for example potassium fluoride on alumina and phase transfer catalysis or by treating reagents 4 with a strong base, such as sodium hydride or sodium hydroxide, followed by the addition of reagents 3. Reduction of the nitro group, for example by Raney nickel catalyzed reduction, followed by saponification of the ester or oxidation of the aldehyde gives, after acidification (if necessary), an intermediate amino acid 5 that may be cyclized to lactam 2 by refluxing in an inert solvent such as xylenes or hexanes.

Scheme 2



Reagents of Formula B are either commercially available or may be prepared using known procedures. For example, suitably mono-protected piperazines may be reacted with a compound of the formula Y-C_{2-5}alkyl or Y-$(CH_2)_n$OP, where Y is a leaving group such as halo and P is a suitable protecting group, in the presence of a base in an inert solvent, followed by removal of the protecting groups.

In some cases the chemistries outlined above may have to be modified, for instance by use of protective groups, to prevent side reactions due to reactive groups,

such as reactive groups attached as substituents. This may be achieved by means of conventional protecting groups, for example as described in "Protective Groups in Organic Chemistry" McOmie, J.F.W. Ed., Plenum Press, 1973 and in Greene, T.W. and Wuts, P.G.M., "Protective Groups in Organic Synthesis", John Wiley & Sons, 1991.

The formation of a desired compound salt is achieved using standard techniques. For example, the neutral compound is treated with an acid in a suitable solvent and the formed salt is isolated by filtration, extraction or any other suitable method. The conversion of a given compound salt to a desired compound salt is achieved by applying standard techniques, in which an aqueous solution of the given salt is treated with a solution of base, e.g. sodium carbonate or sodium or potassium hydroxide, to liberate the free base which is then extracted into an appropriate solvent, such as ether. The free base is then separated from the aqueous portion, dried and treated with the requisite acid as described above to give the desired salt.

The formation of solvates of the compounds of the invention will vary depending on the compound and the solvate. In general, solvates are formed by dissolving the compound in the appropriate solvent and isolating the solvate by cooling or using an antisolvent. The solvate is typically dried or azeotroped under ambient conditions.

Prodrugs of the compounds of the invention may be conventional esters formed with available hydroxy, amino or carboxyl group. For example, when R^2 is $(CH_2)_nOH$ in a compound of Formula I, it may be acylated using an activated acid in the presence of a base, and optionally, in inert solvent (e.g. an acid chloride in pyridine). Some common esters which have been utilized as prodrugs are phenyl esters, aliphatic (C_8-C_{24}) esters, acyloxymethyl esters, carbamates and amino acid esters.

A radiolabeled compound of the invention may be prepared using standard methods known in the art. For example, tritium may be incorporated into a

compound of the invention using standard techniques, for example by hydrogenation of a suitable precursor to a compound of the invention using tritium gas and a catalyst. Alternatively, a compound of the invention containing radioactive iodo may be prepared from the corresponding trialkyltin (suitably trimethyltin) derivative using standard iodination conditions, such as [^{125}I] sodium iodide in the presence of chloramine-T in a suitable solvent, such as dimethylformamide. The trialkyltin compound may be prepared from the corresponding non-radioactive halo, suitably iodo, compound using standard palladium-catalyzed stannylation conditions, for example hexamethylditin in the presence of tetrakis(triphenylphosphine) palladium (0) in an inert solvent, such as dioxane, and at elevated temperatures, suitably 50-100°C.

4. Pharmaceutical Compositions

The compounds of the invention are preferably formulated into pharmaceutical compositions for administration to human subjects in a biologically compatible form suitable for administration *in vivo*. Accordingly, in another aspect, the present invention provides a pharmaceutical composition comprising a compound of Formula I in admixture with a suitable diluent and/or carrier.

The compositions containing the compounds of the invention can be prepared by known methods for the preparation of pharmaceutically acceptable compositions which can be administered to subjects, such that an effective quantity of the active substance is combined in a mixture with a pharmaceutically acceptable vehicle. Suitable vehicles are described, for example, in Remington's Pharmaceutical Sciences (Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., USA 1985 and each of its later editions published to date). On this basis, the compositions include, albeit not exclusively, solutions of the substances in association with one or more pharmaceutically acceptable vehicles and/or diluents, and are contained in buffered solutions with a suitable pH and are iso-osmotic with the physiological fluids.

In accordance with the methods of the invention, the described compounds or salts or solvates thereof may be administered to a patient in a variety of forms depending on the selected route of administration, as will be understood by those skilled in the art. The compositions of the invention may be administered orally or parenterally. Parenteral administration includes intravenous, intraperitoneal, subcutaneous, intramuscular, transepithelial, nasal, intrapulmonary, intrathecal, rectal and topical modes of administration. Parenteral administration may be by continuous infusion over a selected period of time.

A compound of the invention or a salt or solvate thereof may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsules, or it may be compressed into tablets, or it may be incorporated directly with the food of the diet. For oral therapeutic administration, the compound of the invention may be incorporated with excipient and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like.

A compound of the invention may also be administered parenterally or intraperitoneally. Solutions of a compound of the invention as a free base or pharmacologically acceptable salt or solvate can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, DMSO and mixtures thereof with or without alcohol, and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms. A person skilled in the art would know how to prepare suitable formulations. Conventional procedures and ingredients for the selection and preparation of suitable formulations are described, for example, in Remington's Pharmaceutical Sciences (1990 - 18th edition) and in The United States Pharmacopeia: The National Formulary (USP 24 NF19) published in 1999.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersion and sterile powders for the extemporaneous preparation of

sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy syringability exists.

The compounds of the invention may be administered to an animal alone or in combination with pharmaceutically acceptable carriers and/or diluents, as noted above, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard pharmaceutical practice.

Preferably, the composition is in unit dose form such as a tablet, capsule or ampoule. Suitable unit doses, i.e. therapeutically effective amounts, can be determined during clinical trials designed appropriately for each of the conditions for which administration of a chosen compound is indicated and will of course vary depending on the desired clinical endpoint. It is anticipated that dosage sizes appropriate for administering the compounds of the invention will be roughly equivalent to those used currently for clozapine. Accordingly, each dosage unit for oral administration may contain from about 1 mg to about 500 mg, preferably from about 5 mg to about 450 mg, more preferably from about 10 mg to about 400 mg, even more preferably from about 15 mg to about 350 mg and most preferably from about 20 mg to about 300 mg and will be administered in a frequency appropriate for initial and maintenance treatments. In particular, on a routine basis, compounds of Formula I, will need to be given in a high concentration, the concentration which would bring the occupancy into the same range as other psychotic drugs. However, in the body of the recipient things are dynamic, and in the face of dynamic fluxes of dopamine these drugs with a fast K_{off} lead to a faster approach to equilibrium as well as more competitive displacement by dopamine.

5. Uses

The present invention provides a new range of treatments of patients with psychotic disorders, preferably dopamine-related neuropsychiatric disorders. Accordingly, the present invention provides a method of treating neuropsychiatric disorders (including, but not limited to, conditions associated with or leading to psychosis, emotional and behavioral disturbances, schizophrenia and schizophrenia

spectrum disorders, psychotic disorders in the context of affective disorders, depression, psychosis disorders induced by drugs/medication (such as Parkinson's psychosis), drug induced movement disorders (dyskinesias in Parkinson's disease), psychosis and behavioral disorders in the context of dementias and psychotic disorders due to a general medical conditions, or combinations thereof), comprising administering to a subject in need thereof an effective amount of a compound of Formula I. Preferably, the subject is a human or an animal (e.g., a dog) and the compound of Formula I is combined with a pharmaceutically acceptable carrier and/or diluent to provide a dosage composition as described hereinabove.

While not wishing to be bound to any one theory, it is hypothesized that it is the low receptor occupancy of the D_2 receptor with a drug having a high Ki and/or fast K_{off}, which explain the "atypicality" of the compounds of the present invention. Affinity (more precisely, K_i) is, by definition, the ratio of K_{off} / K_{on} (the rate at which the drug moves off of and on to the receptor). In theory, either a difference in K_{on} and/or a difference in K_{off} could lead to low affinity. To examine where K_{on} or K_{off} drives the differences in D_2 affinity between typical and atypical antipsychotics, the affinity, K_{on} and K_{off} were measured for a series of typical and atypical antipsychotics (Kapur and Seeman 2000a). Although affinity for the D_2 receptor varied nearly a thousand-fold, from 0.025 nM for nemonapride to 155 nm for quetiapine, 99% of the difference in affinity of the antipsychotics was driven by differences in their K_{off} at the D_2 receptor. Differences in K_{on} did not account for any significant differences in affinity. All antipsychotics (typical or atypical) attach to the D_2 receptor with a similar rate constant; they typically differ only in how fast they come off of the receptor. It is proposed that this relationship between fast K_{off} and low affinity is an important underlying molecular feature that explains why low affinity at the D_2 receptor leads to the atypical antipsychotic effect with diminished or without the "typical" antipsychotic side effect profile. This theory also explains why drugs like risperidone and olanzapine do not act as atypical as clozapine (since their K_{off} is not as fast). Furthermore, this hypothesis has the ability to explain one fact that no previous hypothesis can explain, why drugs like remoxipride and amisulpride, which are pure D_2 / D_3 antagonists demonstrate features of atypical antipsychotics. However, there is

a limit to how fast one would want K_{off}. Water, theoretically, has one of the fastest K_{off} on the dopamine receptor. While it does not give rise to side-effects, it is also not efficacious. Since some element of D_2 occupancy is essential to obtain antipsychotic effect, there is an optimal value of K_{off} which maximizes response with minimal side-effects.

The compounds of Formula I are useful since they demonstrate characteristics of atypical antipsychotic drugs with diminished or without the typical side effect antipsychotic drug profile. The compounds of Formula I are expected to provide improved psychotic symptoms without EPS with secondary improvement in negative symptoms, mood and cognition. While not wishing to limit the full range of disorders in animals which will benefit, compounds of Formula I are expected to be useful in conditions associated with or leading to psychosis and emotional and behavioral disturbances, including but not limited to schizophrenia and schizophrenia spectrum disorders; psychotic disorders in the context of affective disorders such as depression; psychotic disorders induced by drugs/medications (such as Parkinson's psychosis); drug-induced movement disorders (dyskinesias in Parkinson's Disease); psychotic and behavioral disorders in the context of dementias; and psychotic disorders due to a general medical condition.

As herein before mentioned, the side effect of agranulocytosis has limited the use of clozapine, the most effective antipsychotic (in terms of efficacy and "atypicality") to being the drug of last resort. The best of current evidence suggests that clozapine's agranulocytosis is linked to its reactive metabolites (Uetrecht 1996). Furthermore, studies suggest that if one uses the tricyclic structure with an oxygen (dibenzoxazepine) or sulphur bridge (dibenzothiazepine) instead of the nitrogen (dibenzazepines) these reactive metabolites can be avoided (Uetrecht et al. 1997). This is supported by evidence that drugs which are similar to clozapine but avoid the dibenzazepine, e.g. the dibenzoxazepines such as loxapine and amoxapine, have never been implicated in agranulocytosis despite many years of use in high doses (Jegouzo et al. 1999). The compounds of the present invention, being oxazepines and thiazepines, are not expected to have the agranulocytosis side effect.

As hereinbefore mentioned, the inventors have prepared novel compounds of Formula I. Accordingly, the present invention includes all uses of the compounds of the invention including their use in therapeutic methods and compositions as antipsychotics, their use in diagnostic assays and their use as research tools.

The present invention further includes the use of a compound of Formula I to treat neuropsychiatric disorders, preferably a psychosis, more preferably schizophrenia and schizophrenia spectrum disorders. The present invention further includes a use of a compound or a composition of the invention to prepare a medicament for use to treat neuropsychiatric disorders, preferably a psychosis, more preferably schizophrenia and schizophrenia spectrum disorders.

The compounds of the invention can be used alone or in combination with other agents that have antipsychotic activity or in combination with other types of treatment (which may or may not have antipsychotic activity) for psychotic disorders. In a particular aspect of the present invention, the compounds of the invention may be used in combination with other therapies and therapeutics to treat schizophrenia and schizophrenia spectrum disorders.

In addition to the above-mentioned therapeutic uses, the compounds of the invention are also useful in diagnostic assays, screening assays and as research tools.

In a specific embodiment, the present invention provides a method of treating neuropsychiatric disorders, preferably a psychosis, more preferably schizophrenia and schizophrenia spectrum disorders, comprising administering to an animal in need thereof, a therapeutically effective amount of a compound selected from the group of compounds:

(A-1) 8-Trifluoromethyl-11-(4-ethylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-2) 8-Trifluoromethyl-11-(4-(2'-hydroxyethyl)piperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-3) 8-Trifluoromethyl-11-(4-propylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-3a) 8-Trifluoromethyl-11-(4-propylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine•HCl;

(A-4) 8-Trifluoromethyl-11-(4-isopropylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-4a) 8-Trifluoromethyl-11-(4-isopropylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine•HCl;

(A-5) 8-Trifluoromethyl-11-(4-butylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-5a) 8-Trifluoromethyl-11-(4-butylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine•HCl;

(A-6) 8-Chloro-11-(4-ethylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-6a) 8-Chloro-11-(4-ethylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine•HCl;

(A-7) 8-Chloro-11-(4-(2'-hydroxyethyl)piperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-8) 8-Chloro-11-(4-propylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-9) 8-Chloro-11-(4-isopropylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-10) 8-Chloro-11-(4-butylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-11) 8-Fluoro-11-(4-ethylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-12) 8-Chloro-11-(4-ethylpiperazin-1-yl)-dibenzo [b,f][1,4]thiazepine;

(A-13) 8-Chloro-11-(4-(2'-hydroxyethyl)piperazin-1-yl)-dibenzo[b,f][1,4]thiazepine;

(A-14) 8-Chloro-11-(4-propylpiperazin-1-yl)-dibenzo[b,f][1,4]thiazepine;

(A-14a) 8-Chloro-11-(4-propylpiperazin-1-yl)-dibenzo[b,f][1,4]thiazepine•HCl;

(A-15) 8-Chloro-11-(4-isopropylpiperazin-1-yl)-dibenzo[b,f][1,4]thiazepine•HCl;

(A-15a) 8-Chloro-11-(4-isopropylpiperazin-1-yl)-dibenzo[b,f][1,4]thiazepine•HCl;.

(A-16) 8-Chloro-11-(4-butylpiperazin-1-yl)-dibenzo[b,f][1,4]thiazepine; and

(A-16a) 8-Chloro-11-(4-butylpiperazin-1-yl)-dibenzo[b,f][1,4]thiazepine•HCl.

More specifically the present invention provides a method of treating neuropsychiatric disorders, preferably a psychosis, more preferably schizophrenia and schizophrenia spectrum disorders, comprising administering to an animal in need thereof, a therapeutically effective amount of a compound selected from the group of compounds:

(A-1) 8-Trifluoromethyl-11-(4-ethylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-2) 8-Trifluoromethyl-11-(4-(2'-hydroxyethyl)piperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-6) 8-Chloro-11-(4-ethylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-6a) 8-Chloro-11-(4-ethylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine•HCl;

(A-7) 8-Chloro-11-(4-(2'-hydroxyethyl)piperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-11) 8-Fluoro-11-(4-ethylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-12) 8-Chloro-11-(4-ethylpiperazin-1-yl)-dibenzo [b,f][1,4]thiazepine; and

(A-13) 8-Chloro-11-(4-(2'-hydroxyethyl)piperazin-1-yl)-dibenzo[b,f][1,4]thiazepine.

Even more specifically, the present invention provides a method of treating neuropsychiatric disorders, preferably a psychosis, more preferably schizophrenia and schizophrenia spectrum disorders, comprising administering to an animal in need thereof, a therapeutically effective amount of a compound selected from the group of compounds:

(A-6) 8-Chloro-11-(4-ethylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-6a) 8-Chloro-11-(4-ethylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine•HCl;

(A-7) 8-Chloro-11-(4-(2'-hydroxyethyl)piperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-12) 8-Chloro-11-(4-ethylpiperazin-1-yl)-dibenzo [b,f][1,4]thiazepine; and

(A-13) 8-Chloro-11-(4-(2'-hydroxyethyl)piperazin-1-yl)-dibenzo[b,f][1,4]thiazepine.

Most specifically, the present invention provides a method of treating neuropsychiatric disorders, preferably a psychosis, more preferably schizophrenia and schizophrenia spectrum disorders, comprising administering to an animal in need thereof, a therapeutically effective amount of a compound selected from the group of compounds:

(A-6) 8-Chloro-11-(4-ethylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;

(A-6a) 8-Chloro-11-(4-ethylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine•HCl; and

(A-7) 8-Chloro-11-(4-(2'-hydroxyethyl)piperazin-1-yl)-dibenzo[b,f][1,4]oxazepine.

Preferably, the animal is a human and the compound is combined with a pharmaceutically acceptable carrier and/or diluent to provide a dosage composition as described hereinbefore.

The following non-limiting examples are illustrative of the present invention:

EXAMPLES

Example 1. 8-Trifluoromethyl-11-(4-ethylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine

8-Trifluoromethyl-10*H*-dibenzo[b,f][1,4]oxazepine-11-one (**2**, X = O, $R^1 = CF_3$) (2.0 g, 7.16 mmol), phosphorus oxychloride (5 mL, 53 mmol), N,N-dimethylaniline (1.0 ml) and toluene (25 mL) were combined and heated to reflux for 3 hours. The mixture was evaporated under vacuum to afford the imino chloride intermediate **A**, X = O $R^1 = CF_3$). This was used in the next step without further purification. Toluene 25 (25 ml) was added followed by 5 ml (45 mmol) of 1-ethylpiperazine. This mixture was refluxed for 3 hours. After evaporation the residue was added to a saturated aqueous K_2CO_3, which was extracted with chloroform. The chloroform phase was dried over magnesium sulfate, filtered and the solvent removed to give a viscous liquid. This was purified by flash chromatography on silica gel, eluting with 9:1 hexane: ethyl acetate, then 1:1 hexane: ethyl acetate and finally 100 % ethyl acetate. Recrystallization from n-heptane gave the product as yellow crystals, mp 76-77 °C, ^1H NMR (300 MHz, $CDCl_3$) δ1.16 (t, 3H, J = 7.2 Hz, CH_3), 2.55 (q, 2H, J = 7.2 Hz, $-CH_2-$), 2.59 (broad s, 4H, $-CH_2-$), 3.65 (broad s, 4H, $-CH_2-$), 7.20-7.25 (m, 2H), 7.27-7.30 (m, 2H), 7.35-7.39 (dd, J = 1.5 and 7.5 Hz, 1H), 7.43 (broad s, 1H), 7.46 - 7.52 (ddd, J = 1.8, 7.2, 8.1 Hz, 1H), MS (EI) m/z 375 (M^+, 4.2%), 304 (8.5), 303 (15.1), 292 (5.8), 291 (25.5), 263 (6.9), 262 (18.4), 84 (100), 70 (5.0). HRMS calcd for $C_{20}H_{20}N_3OF_3$ 375.1558, found 375.1557.

Example 2. 8-Trifluoromethyl-11-(4-(2'-hydroxyethyl)piperazin-1-yl)-dibenzo[b,f][1,4]oxazepine

Prepared in the same manner as Example 1 with 1-(2'-hydroxyethyl)piperazine. mp 110-111°C, ^1H NMR (300 MHz, $CDCl_3$) δ1.59 (broad s, 1H, -OH), 2.61 - 2.65 (overlapping broad s and t, 6H), 3.62 (broad s, 4H, $-CH_2-$), 3.67 (t, 2H, $-CH_2OH$), 7.20-7.25 (m, 2H), 7.27-7.30 (m, 2H), 7.35-7.39 (dd, J = 1.5 and 7.5 Hz, 1H), 7.43 (broad s, 1H), 7.46 - 7.52 (ddd, J = 1.8, 7.2, 8.1 Hz, 1H), MS (EI) m/z 391 (M^+,

2.1%), 292(8.20), 291(34.0), 263(8.3), 262(22.4), 113(45.1), 101(13.0), 100(100), 70(11.5), 70(9.8). HRMS calcd for $C_{20}H_{20}N_3O_2F_3$ 391.1508, found 391.1489.

Example 3. 8-Trifluoromethyl-11-(4-propylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine•HCl

Prepared in the same manner as Example 1 using 1-propylpiperazine, except that the residue obtained after flash chromatography was dissolved in ethyl acetate and the HCl salt precipitated as a white solid by the addition of 1M HCl in ether. Mp 110 (decomposes), ^{1}H NMR (300 MHz, DMSO-d^6) δ0.90 (t, 3H, $-CH_3$), 1.17 (m, 2H,-CH_2-), 3.02 (m, 6H, piperazine -CH_2- and propyl -CH_2), 3.51 (broad s, 4H, -CH_2), 7.35-7.5 (m, 5H, overlapping Ar-H), 7.57 (dd, 1H, J = 1.5 Hz and 7.5 Hz), 7.69 (doublet of triplets, 1H, J = 1.5 Hz and 8 Hz), 10.96 (s, 1H, N^+H), MS (EI) m/z 389 (M^+ for free base, 4.9%), 303 (13.0), 291 (15.9), 193 (9.3), 111 (64.4), 98 (100), 56 (21.7). HRMS calcd for $C_{21}H_{22}N_3OF_3$ 389.1715, found 389.1713.

Example 4. 8-Trifluoromethyl-11-(4-isopropylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine•HCl

Prepared following the procedure of Example 3 using 1-isopropylpiperazine and had a mp 270 °C (decomposes), ^{1}H NMR (300 MHz, DMSO-d^6) δ1.20 (d, 6H, J 6.6 Hz), 3.20 (broad s, 4H, -CH_2-), 3.45 (overlapping broad s and multiplet, 5H, -CH and -CH_2-), 7.35-7.45 (m, 5H, overlapping Ar-H), 7.57 (dd, 1H, J = 1.5 Hz and 7.5 Hz), 7.64 (doublet of triplets, 1H, J = 1.5 Hz and 8 Hz), 10.8 (s, 1H, N^+H), MS (EI) m/z 389 (M^+ for free base, 10.4%), 303 (21.0), 291 (16.3), 193 (13.3), 125 (74.1), 111 (58.5), 98 (100), 56 (37.7). HRMS calcd for $C_{21}H_{22}N_3OF_3$ 389.1715, found 389.1715.

Example 5. 8-Trifluoromethyl-11-(4-butylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine•HCl

Prepared following the procedure of Example 3 with 1-butylpiperazine and had a mp 240 °C (decomposes), ^{1}H NMR (300 MHz, DMSO-d^6) δ0.91 (t, 3H, J = 7.5 Hz, -

CH_3), 1.31 (m, 2H, -CH_2), 1.65 (m, 2H, -CH_2), 3.10 (broad s, 4H, -CH_2), 3.4 - 3.5 (overlapping multiplets, 6H, piperazinyl -CH_2- and butyl N-CH_2), 7.35-7.45 (m, 5H, overlapping Ar-H), 7.51 (dd, 1H, J = 1.5 Hz and 7.5 Hz), 7.63 (doublet of triplets, 1H, J = 1.5 Hz and 8 Hz), 10.2 (s, 1H, N^+H), MS (EI) m/z 403 (M^+ for free base, 6.3%), 303 (18.5), 291 (17.7), 193 (12.4), 125 (74.1), 112 (100), 70 (37.1), 56 (6.9). HRMS calcd for $C_{22}H_{24}N_3OF_3$ 403.1871, found 403.1858.

Example 6. 8-Chloro-11-(4-ethylpiperazin-1-yl)-dibenzo[b,f][1,4] oxazepine (1b) and 8-chloro-11-(4-ethylpiperazin-1-yl) -dibenzo [b,f][1,4]oxazepine•HCl

8-Chloro-10*H*-dibenzo[b,f][1,4]oxazepin-11-one (2, X = O, R^1 = Cl) (6.0 g, 24.4 mmol), phosphorus oxychloride (20 mL, 212 mmol), N,N-dimethylaniline (3.0 ml) and toluene (100 mL) were combined and heated to reflux for 3 hours. After evaporation, the residue was dissolved in 50 mls of toluene, 21.7 ml (170 mmol) of 1-ethylpiperazine was added and the mixture was refluxed for 3 hours. After evaporation, the residue was added to saturated aqueous K_2CO_3, which was extracted with chloroform. The chloroform phase was dried over $MgSO_4$, and after filtration the chloroform was evaporated to give a viscous liquid which was purified by flash chromatography on silica gel (9:1 hexane: ethyl acetate, then 1:1 hexane: ethyl acetate and finally 100 % ethyl acetate). The crude free base form of the product was a low melting solid that had ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (t, 3H, CH_3), 2.45 - 2.60 (broad m, 6H, piperazinyl CH_2 and ethyl CH_2), 3.65 (broad s, 4H, CH_2), 6.92 (dd, 1H, J = 2.5 and 8.5 Hz), 7.08 (d, 1H, J = 8.5 Hz), 7.14 (d, 1H, J = 2.5 Hz), 7.22 (doublet of triplets, 1H, J = 1.6 and 7.6 Hz), 7.25 (dd, 1H, 1.4 and 8.1 Hz), 7.36 (dd, 1H, J = 1.9 and 7.7 Hz), 7.48 (ddd, 1H, J = 1.9, 7.7, 8.1 Hz). The solid was converted to the HCl salt by dissolving in ethyl acetate and adding 1N HCl. This gave a white solid (3.8 g, 43%), mp. 280 (decomposes), ^1H NMR (300 MHz, DMSO-d^6) δ 1.24 (t, 3H, -CH_3), 3.18 (q, 2H, CH_2), 3.2-3.3 (broad, 4H, piperazinyl CH_2), 3.6-3.7 (Broad, 4H, piperazinyl CH_2), 7.07 - 7.13 (2H, m, overlapping coupled pair), 7.26 (dd, 1H, J = 0.9 and 8.0 Hz), 7.36 (doublet of triplets, 1H, J = 1.5 and 8.2 Hz), 7.43 (dd, 1H, 1.2

and 8.1 Hz), 7.52 (dd, 1H, 1.8 and 8.4 Hz), 7.64 (ddd, 1H, J = 1.8, 8.0 and 8.4 Hz), MS (EI) m/z 341 (M^+ for free base, 14.9%), 269(15.3), 257(41.5), 228(6.8), 193(24.3), 97(85.4), 84(100), HRMS calcd for $C_{19}H_{20}N_3OCl$ 341.1295, found 341.1297.

Example 7. 8-Chloro-11-(4-(2'-hydroxyethyl)piperazin-1-yl)-dibenzo[b,f][1,4]oxazepine

This was prepared in the same manner as Example 6 using 1-(2'-hydroxyethylpiperazine). The free base obtained by flash chromatography was recrystallized from 10: 1 hexane: ethyl acetate to give yellow crystals of mp 149-150 ^oC, ^1H NMR (300 MHz, $CDCl_3$), δ 1.66 (s, 1H, OH), 2.65 - 2.75 (m, 6H, overlapping $-CH_2-$ peaks), 3.62 (broad s, 4H, piperazinyl CH_2), 3.68 (t, 2H, J = 5.4 Hz), 6.92 (dd, 1H, J = 2.5 and 8.5 Hz), 7.04 (d, 1H, J = 8.5 Hz), 7.12 (d, 1H, J = 2.5 Hz), 7.20 (doublet of triplets, 1H, J = 1.6 and 7.6 Hz), 7.24 (dd, 1H, 1.4 and 8.1 Hz), 7.34 (dd, 1H, J = 1.9 and 7.7 Hz), 7.46 (ddd, 1H, J = 1.9, 7.7, 8.1 Hz), MS (EI) m/z 357 (M^+, 2.0%), 229(6.5), 228(21.6), 113(45.9), 101(10.7), 100(100), 70(10.1), 69(10.8), HRMS calcd for $C_{19}H_{20}N_3O_2Cl$ 357.1244, found 357.1254.

Example 8. 8-Chloro-11-(4-propylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine

Prepared in the same manner as Example 7 with 1-propylpiperazine and had a mp 90 - 91 ^oC, ^1H NMR (300 MHz, $CDCl_3$), δ 0.93 (t, 3H, J = 7.7 Hz, CH_3), 1.58 (m, 2H, CH_2), 2.39, (t, 2H, CH_2N), 2.55 - 2.65 (broad s, 4H, piperazinyl CH_2), 3.55-3.65 (broad s, 4H, piperazinyl CH_2), 6.89 (dd, 1H, J = 2.5 and 8.5 Hz), 7.03 (d, 1H, J = 8.5 Hz), 7.12 (d, 1H, J = 2.5 Hz), 7.21 (doublet of triplets, 1H, J = 1.6 and 7.6 Hz), 7.24 (dd, 1H, 1.4 and 8.1 Hz), 7.33 (dd, 1H, J = 1.9 and 7.7 Hz), 7.45 (ddd, 1H, J = 1.9, 7.7, 8.1 Hz), MS (EI) m/z 355 (M^+, 11.0%), 269(15.7), 257(32.1), 228(15.7), 193(21.5), 111(80.3), 98(100), HRMS calcd for $C_{20}H_{22}N_3OCl$ 355.1451, found 355.1457.

Example 9. 8-Chloro-11-(4-isopropylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine

Prepared in the same manner as Example 7 with 1-isopropylpiperazine and had a mp 55-56 ^{o}C, ^{1}H NMR (300 MHz, $CDCl_3$), δ 1.08 (d, 6H, J = 6.6 Hz, CH_3), 2.55 - 2.65 (broad s, 4H, piperazinyl CH_2), 2.74 (septet, 1H, J = 6.6 Hz, CH), 3.55-3.65 (broad s, 4H, piperazinyl CH_2), 6.89 (dd, 1H, J = 2.5 and 8.5 Hz), 7.02 (d, 1H, J = 8.5 Hz), 7.12 (d, 1H, J = 2.5 Hz), 7.19 (doublet of triplets, 1H, J = 1.6 and 7.6 Hz), 7.24 (dd, 1H, 1.4 and 8.1 Hz), 7.33 (dd, 1H, J = 1.9 and 7.7 Hz), 7.44 (ddd, 1H, J = 1.9, 7.7, 8.1 Hz), MS (EI) m/z 355 (M^+, 7.8%), 269(15.7), 257 (17.0), 245(10.8), 228(11.8), 193(19.7), 111(61.0), 98(100), 56 (46.5), HRMS calcd for $C_{20}H_{22}N_3OCl$ 355.1451, found 355.1470.

Example 10. 8-Chloro-11-(4-butylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine

Prepared in the same manner as Example 7 with 1-butylpiperazine and had a mp 97-98 ^{o}C, ^{1}H NMR (300 MHz, $CDCl_3$), δ 0.93 (t, 3H, J = 7.5 Hz, CH_3), 1.35 (sextet, 2H, CH_2), 1.46 (quintet, 2H, CH_2), 2.40 (t, 2H, NCH_2), 2.55 - 2.65 (broad s, 4H, piperazinyl CH_2),3.55-3.65 (broad s, 4H, piperazinyl CH_2), 6.89 (dd, 1H, J = 2.5 and 8.5 Hz), 7.02 (d, 1H, J = 8.5 Hz), 7.12 (d, 1H, J = 2.5 Hz), 7.19 (doublet of triplets, 1H, J = 1.6 and 7.6 Hz), 7.24 (dd, 1H, 1.4 and 8.1 Hz), 7.33 (dd, 1H, J = 1.9 and 7.7 Hz), 7.44 (ddd, 1H, J = 1.9, 7.7, 8.1 Hz), MS (EI) m/z 369 (M^+, 8.7%), 291 (30.5), 269 (15.1), 257 (24.8), 228(13.8), 193(25.0), 125(78.9), 112(100), 70(40.9), HRMS calcd for $C_{21}H_{24}N_3OCl$ 369.1608, found 369.1604.

Example 11. 8-Fluoro-11-(4-ethylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine

Prepared in the same manner as Example 1 starting with 8-fluoro-10*H*-dibenzo[b,f][1,4]oxazepin-11-one (**2**, X = O, R^1 = F) with 1-ethyl piperazine. This compound was an oil with ^{1}H NMR (400 MHz, $CDCl_3$), δ1.16 (t, 3H, J = 7.2 Hz, CH_3), 2.55 (q, 2H, J = 7.2 Hz, $-CH_2-$), 2.55-2.65 (broad s, 4H, piperazinyl CH_2),

3.55-3.65 (broad s, 4H, piperazinyl CH_2), 6.64 (ddd, 1H, J = 2.4, 6.6 and 7.2 Hz), 6.82 (dd, 1H, J = 2.1 and 7.5 Hz), 7.12 (dd, 1H, J = 4.2 and 6.2 Hz), 7.21 (doublet of triplets, 1H, J = 0.8 and 6.0 Hz), 7.23 (dd, 1H, J = 0.9 and 6.3 Hz), 7.34 (dd, 1H, J = 1.2 and 5.7 Hz), 7.44 (doublet of triplets, 1H, J = 1.2 and 6.0 Hz).

Example 12. 8-Chloro-11-(4-ethylpiperazin-1-yl)-dibenzo [b, f] [1, 4] thiazepine

8-Chloro-*10*H-dibenzo[b,f][1,4]thiazepin-11-one **2** (X = S and R^1 = Cl) (0.5 g, 1.91 mol), phosphorus oxychloride (5 ml, 53 mmol), toluene (25 ml) and N,N-dimethylaniline (1.0 ml) were heated at reflux for 3 hours. After evaporation of the volatiles, 25 ml of toluene and 5 ml (45 mmol) of 1-ethylpiperazine were added. Work-up and purification as described in Example 1 gave 150 mg (22%) of light yellow crystals, mp 100-101 °C, ^{1}H NMR (300 MHz, $CDCl_3$), δ1.11 (t, 3H, J = 6.0 Hz, CH_3), 2.55 (q, 2H, J = 6.0 Hz, -CH_2-), 2.55-2.65 (broad s, 4H, piperazinyl CH_2), 3.55-3.65 (broad s, 4H, piperazinyl CH_2), 6.83 (dd, 1H, J = 1.5 and 6.0 Hz), 7.07 (d, 1H, J = 1.5 Hz), 7.25 - 7.40 (mult., 4H), 7.50 (dd, 1H, J = 7.5 Hz), MS (EI) m/z 357 (M^+, 16.1%), 244(34.2), 209(30.1), 97(93.7), 84(100), HRMS calcd for $C_{19}H_{20}N_3SCl$ 357.1066, found 357.1067.

Example 13. 8-Chloro-11-(4-(2'-hydroxyethyl)piperazin-1-yl)-dibenzo[b,f][1,4] thiazepine

Prepared following the procedure of Example 12 using 1-(2'-hydroxyethyl)piperazine and had mp 110 - 111 °C, ^{1}H NMR (300 MHz, $CDCl_3$), δ 2.55-2.65 (broad s, 4H, piperazinyl CH_2), 2.64 (t, 2H, J = 7.5 Hz, CH_2-), 3.55-3.65 (broad s, 4H, piperazinyl CH_2), 3.68 (t, 2H, J = 7.5 Hz, -CH_3OH), 6.88 (dd, 1H, J = 1.5 and 6.0 Hz), 7.11 (d, 1H, J = 1.5 Hz), 7.30 - 7.40 (mult., 4H), 7.54 (dd, 1H, J = 7.5 Hz), MS (EI) m/z 373 (M^+, 6.1%), 244(53.9), 209(47.0), 113(42.0), 100(100), HRMS calcd for $C_{19}H_{20}N_3OSCl$

Example 14. 8-Chloro-11-(4-propylpiperazin-1-yl)-dibenzo[b,f][1,4]thiazepine•HCl

Prepared using the procedure of Example 12 using 1-propylpiperazine, the HCl salt being obtained by dissolving the residue obtained from flash chromatography in ethyl acetate and precipitating the salt with 1N HCl in ether. The salt was a hygroscopic white solid with ^{1}H NMR (300 MHz, DMSO-d^6), δ 0.90 (t, 3H, CH_3), 1.70 (m, 2H, -CH_2-), 3.00 (t, 2H, -CH_2N), 3.0-3.1 (broad s, 4H, piperazinyl CH_2), 3.5-3.6 (broad s, 4H, piperazinyl CH_2), 7.00 (dd, 1H, J = 2.1 and 8.4 Hz), 7.07 (d, 1H, J = 2.1 Hz), 7.40 (d, 1H, J = 8.4 Hz), 7.5-7.6 (m, 4H), 10.7 (s, 1H, N^+H), MS (EI) m/z 371 (M^+ for free base, 55.1%), 286(51.0), 244 (30.2), 209(23.6), 111 (19.1), 97(100), HRMS calcd for $C_{20}H_{22}N_3SCl$ 371.1223, found 371.1233.

Example 15. 8-Chloro-11-(4-isopropylpiperazin-1-yl)-dibenzo[b,f][1,4]thiazepine•HCl

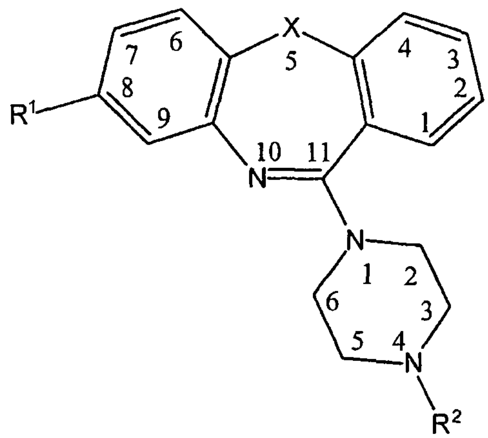
Prepared using the procedure of Example 12 using 1-isopropylpiperazine, the HCl salt being obtained by dissolving the residue obtained from flash chromatography in ethyl acetate and precipitating the salt with 1N HCl in ether. The salt had a mp 140 (decomposes), ^{1}H NMR (300 MHz, DMSO-d^6), δ 1.31 (d, 6H, CH_3), 3.0-3.1 (broad s, 4H, piperazinyl CH_2), 3.3 (septet, 1H, CH), 3.5-3.6 (broad s, 4H, piperazinyl CH_2), 7.02 (dd, 1H, J = 2.1 and 8.4 Hz), 7.11 (d, 1H, J = 2.1 Hz), 7.43 (d, 1H, J = 8.4 Hz), 7.5-7.6 (m, 4H), 11.0 (s, 1H, N^+H), MS (EI) m/z 371 (M^+ for free base, 7.2 %), 286(13.1), 244 (18.6), 209(25.7), 111 (66.8), 98(100), HRMS calcd for $C_{20}H_{22}N_3SCl$ 371.1223, found 371.1234.

Example 16. 8-Chloro-11-(4-butylpiperazin-1-yl)-dibenzo[b,f][1,4]thiazepine•HCl

Prepared using the procedure of Example 12 using 1-butylpiperazine, the HCl salt being obtained by dissolving the residue obtained from flash chromatography in ethyl acetate and precipitating the salt with 1N HCl in ether. The salt was a hygroscopic white solid and ^{1}H NMR (300 MHz, DMSO-d^6), δ 0.99 (t, 3H, CH_3), 1.33 (2H, m),

1.69 (2H, m), 3.02 (t, 2H, NCH_2, 3.1-3.2 (broad s, 4H, piperazinyl CH_2), 3.5-3.6 (broad s, 4H, piperazinyl CH_2), 7.02 (dd, 1H, J = 2.1 and 8.4 Hz), 7.11 (d, 1H, J = 2.1 Hz), 7.43 (d, 1H, J = 8.4 Hz), 7.5-7.6 (m, 4H), 9.9 (s, 1H, N^+H).

Table 1: Summary of Examples for Compounds of Formula 1



I

Example #	R^1	R^2	X
1	CF_3	CH_2CH_3	O
2	CF_3	CH_2CH_2OH	O
3	CF_3	$CH_2CH_2CH_3$	O
4	CF_3	$CH(CH_3)_2$	O
5	CF_3	$CH_2CH_2CH_2CH_3$	O
6	Cl	CH_2CH_3	O
7	Cl	CH_2CH_2OH	O
8	Cl	$CH_2CH_2CH_3$	O
9	Cl	$CH(CH_3)_2$	O
10	Cl	$CH_2CH_2CH_2CH_3$	O
11	F	CH_2CH_3	O
12	Cl	CH_2CH_3	S
13	Cl	CH_2CH_2OH	S
14	Cl	$CH_2CH_2CH_3$	S
15	Cl	$CH(CH_3)_2$	S
16	Cl	$CH_2CH_2CH_2CH_3$	S

Example 17. 8-Trifluoromethyl-10*H*-dibenzo[b,f][1,4] oxazepin-11-one (Formula 2, X = O, R^1 = CF_3)

(a) Methyl salicylate (30.4 g, 0.20 mol), 4-fluoro-3-nitrobenzotrifluoride (41.8 g, 0.20 mol), 18-crown-6 (10.6 g, 0.04 mol), 40% w.w potassium fluoride-alumina and acetonitrile (200 ml) were refluxed for 4 hours. After cooling, 500 mls each of water and diethyl ether were added, and the mixture was transferred to a separatory funnel. After vigorous mixing the aqueous layer and alumina sediments were discarded, and the organic phase was washed twice with 200 mls of saturated potassium chloride solution. The organic layer was dried over $MgSO_4$, and after filtration, the volatiles were removed by rotary evaporator to give 50.9 g (74.6% yield) of methyl O-(2-nitro-4-trifluoromethylphenyl)salicylate, mp 56-57 ^oC, ^1H NMR (300 MHz, $CDCl_3$), δ 3.75 (s, 3H), 6.82 (d, 1H, J = 8.7Hz), 7.21 (d, 1H, J = 8.7Hz), 7.40 (t, 1H, J = 7.8 Hz), 7.63 - 7.67 (m, 2H), 8.06 (dd, 1H, J=1.2 Hz, J = 6.0 Hz), 8.25 (d, 1H, J = 1.5 Hz).

(b) Methyl O-(2-nitro-4-trifluoromethylphenyl)salicylate (30.0 g, 0.088 mol) was dissolved in 150 ml of methanol and hydrogenated over Raney nickel (7.5 g) at room temperature and 50 psi pressure for 6 hours. After filtration to remove the catalyst, the methanol was removed and the residue dissolved in tetrahydrofuran (50 ml) and methanol (50 ml), followed by treatment with 5 N NaOH (20 ml) for 3 hours. After concentration in vacuo, the residue was acidified to pH 1-2 with 6 N HCl. The resulting suspension was filtered to give a solid which was recrystallized from n-heptane to provide O-(2-amino-4-trifluoromethylphenyl)salicylic acid as light gray solid, 13.3 g, 50.9%, mp 108-109.

(c) The aminosalicylic acid (17.3 g, 58.2 mmol) was refluxed in 150 ml of xylene for 24 hours with continuous removal of water. The xylene was removed, and the residue was recrystallized from methanol to provide 8-trifluoromethyl-10H-dibenzo[b,f][1,4]oxazepin-11-one as a white solid, mp 246-247 ^oC, ^1H NMR (DMSO-d^6), δ 7.38 - 7.66 (m, 7H), 10.7 (s, 1H, NH).

Example 18. 8-Chloro-10*H*-dibenzo[b,f][1,4] oxazepin-11-one (Formula 2, X = O, R^1 = Cl)

(a) Salicylaldehyde (0.386 mol) was dissolved in anhydrous DMF (300 ml), and allowed to react with 6.84 g of sodium hydride (95%, 0.27 mol). After the reaction was complete, 2,5-dichloronitrobenzene (40 g, 0.208 mol) was added all at once, and the reaction mixture was stirred at 95 - 100 ^{o}C for 22 hours. The DMF is removed and the residue was extracted with 800 mL dichloromethane. The organic phase was washed with 1N NaOH (2 x 500 mL), dried over $MgSO_4$ and evaporated to a brown solid of O-(2-nitro-4-chlorophenyl)salicylaldehyde (48.5g, 83.9%), m. p. 82-83 ^{o}C, ^{1}H NMR (300 MHz, CDCl3), δ 6.88 (d, 1H, J = 8.1Hz), 7.06 (d, 1H, J = 9.0 Hz,), 7.31 (t, 1H, J = 7.5 Hz), 7.54 (qd, 2H, J = 1.2Hz, J = 2.4Hz), 7.97 (dd, 1H, J = 1.8Hz, J = 7.8Hz), 8.04 (d, 1H, J = 2.4Hz), 10.45(d, 1H, J = 0.9 Hz, -CHO).

(b) To a stirred solution of 48.5g of O-(2-nitro-4-chlorophenyl)salicylaldehyde in 200 mL of acetone at room temperature was added 180 mL of chromic acid reagent (100g $Na_2Cr_2O_7$, 153 g of concentrated H_2SO, and sufficient H_2O to make 500 ml total volume) over a period of 15 min. The solution was kept at 50 ^{o}C by cooling during the addition. After the addition was complete, the mixture was stirred for 20 hours. The acetone was removed, the residue was added into a saturated Na_2CO_3 solution. After filtration, the filtrate was neutralized with concentrated HCl to provide a yellow solid of O-(2-nitro-4-chlorophenyl)salicylic acid, 33.74 g (65.8%), mp 155 - 160^{o}, ^{1}H NMR (300MHz, CDCl3), δ 6.887 (d, 1H, J = 9.0 Hz), 7.04 (dd, 1H, J = 0.9Hz, J = 8.1Hz), 7.36 (t, 1H, J = 8.1Hz), 7.48 (dd, 1H, J = 2.7Hz, J = 9.0 Hz), 7.60 (dd, 1H, J = 1.5 Hz, J = 8.1 Hz), 8.01(d, 1H, J = 2.4 Hz), 8.15 (dd, 1H, J = 1.8 Hz, J = 8.1 Hz).

(c) A solution of 33.74 g of O-(2-nitro-4-chlorophenyl)salicylic acid in 150 mL of methanol was hydrogenated over Raney nickel (6.8 g) at room temperature and 30 psi pressure with stirring for 20 hours. The crude amino acid obtained on evaporation of the methanol was refluxed in 150 mL of xylene for 20 hours with continuous removal of water. The xylene solution was cooled and the xylene was removed, the residue was washed with THF, filtered and dried to provide 8-chloro-10H-

3.822 (s, 3H, -OCH3), 6.95 (d, 1H), 7.26 (s, 1H), 7.49 (dd, 1H, J=1.5Hz), 7.45-7.47 (m, 2H), 7.90 (dd, 1H), 8.12 (d, 1H).

(b) A solution of 9.0 g (27.8 mmol) of methyl S-(2-nitro-4-chloromethylphenyl)thiosalicylate in 100 mL of methanol was hydrogenated over Raney nickel (1.12 g) at room temperature and 30 psi pressure with stirring for 17 hours. The residue obtained on evaporation of the methanol was dissolved in chloroform, filtered, dried over $MgSO_4$, filtered, and concentrated in vacuo to provide methyl S-(2-amino-4-chloromethylphenyl)thiosalicylate as a white solid (8.16 g, 55.6%), ^{1}H NMR (300MHz, $CDCl_3$) δ 4.00 (s, 3H, $-OCH_3$), 4.40 (s, 2H, $-NH_2$), 6.77 (dd, 1H, J = 1.2Hz), 6.79 (dd, 1H, J = 2.1Hz), 6.84 (dd, 1H, J = 2.4Hz), 7.15-7.20 (m, 1H), 7.28-7.34 (m, 1H), 7.40 (d, 1H, J = 8.1Hz), 8.006 (dd, 1H, J = 1.5Hz).

(c) 8.16 g Methyl S-(2-amino-4-chloromethylphenyl)thiosalicylate was dissolved in THF (50 mL) and methanol (50 mL), and treated with 5N sodium hydroxide solution (20 mL) with stirring at room temperature for 17 h. The reaction mixture was concentrated in vacuo, diluted with water, and acidified to pH 1-2 with 6N hydrochloric acid. The resulting suspension was filtered, and recrystallized from n-heptane to provide S-(2-amino-4-chloromethylphenyl)thiosalicylic acid as a light gray solid, ^{1}H NMR (300 MHz, $CDCl_3$), δ 6.77 (dd, 1H, J =2.7 Hz, J = 2.1Hz), 6.83 (d, 1H, J = 2.1Hz), 7.18 (t, 1H), 7.367 (s, 1H), 7.32 (t, 1H), 7.38 (d, 1H, J = 8.4Hz), 8.13 (d, 1H, J = 1.8Hz).

(d) S-(2-Amino-4-chloromethylphenyl)thiosalicylic acid was refluxed in 150 mL of xylene for 21 h with continuous removal of H_2O. The xylene was removed, the residue was washed with 95% ethanol, filtered and dried to provide 8-chloro-10H-dibenzo[b,f][1,4]thiazepin-11-one as a white solid of mp 163-165 ^{o}C, ^{1}H NMR (300 MHz, DMSO-d^6),δ 7.22 (dd, 1H, J = 2.4 and 8.5 Hz), 7.28 (d, 1H, J = 2.4 Hz), 7.44 - 7.53 (m, 3H), 7.58 (d, 1H, J = 8.4 Hz), 7.68 (m, 1H), 10.80 (s, 1H).

Example 21 Binding Affinity and K_{off}

A desirable feature of a compound of the present invention is a low affinity and a fast K_{off} (as predicted by low affinity). As mentioned hereinabove a preferred affinity (K_i) is above about 40 nM. Compounds of the invention have been tested for their affinity using the methods described in Seeman et al. (1993) using ^{3}H-raclopride as ligand. The results are provided in Table 2.

Table 2: Summary of Binding Data

Example Number	K_i (nM)
1	258
2	414
3	n/a
4	215
5	250
6	42
7	108
8	23
9	150
10	28
11	n/a
12	63
13	88
14	n/a
15	58
16	n/a

K_i values of various compounds for comparison	
Isoloxapine	20
Loxapine	9.8
Isoclozapine	15
Clozapine	76

n/a = not available.

Example 22: D_2 Receptor Occupancy and Catalepsy

To document the fact that the compounds cross the blood brain barrier, occupancy at the dopamine D_2 receptors using in-vivo occupancy measures was examined in rats. The test compound was injected subcutaneously followed 30 minutes later by an intravenous injection of ^{3}H-raclopride. The animals were sacrificed 1 hour after drug administration. In animals combining occupancy and catalepsy, rats were tested for catalepsy 10 minutes before sacrifice. Animals were sacrificed by decapitation. Striata and cerebella were rapidly dissected, processed and analyzed as described by Kapur et al. (2000b) Compounds which crossed the blood brain barrier and gave predictable dose-response relationships were then tested to see if they gave catalepsy. Catalepsy is the time-honoured animal model to predict the propensity of compounds to give rise to extrapyramidal side-effects in humans. Catalepsy was measured using a grid-test by a rater blind to the treatment-assignment. The time that animals remained immobile was used as an index of catalepsy by transforming raw-scores into catalepsy scores, with a score of 1 as questionable catalepsy and scores of 2-5 reflecting severity of catalepsy (Ahlenius S et al. 1986). To validate this procedure it was first documented that haloperidol (a drug known to give rise to motor side-effects in humans) gave rise to robust catalepsy at doses above 0.25 mg/kg/sc while clozapine (a drug known not to give rise to motor side-effects in humans) did not give rise to catalepsy at doses up to 20 mg/kg/sc.

The compound of Example 6 showed a dose-dependent increase in D_2 occupancy (dose 1-40 mg/kg/sc in acidified saline; occupancy 5-81%, with an ED_{50} of about 5 mg/kg). No animals showed any evidence of motor-side-effects with this compound.

The compound of Example 7 showed a dose-dependent increase in D_2 occupancy (dose 1-40 mg/kg/sc in acidified saline; occupancy 22-75% with an ED_{50} of 10 mg/kg). No animals showed any evidence of motor-side-effects in doses up to 40 mg/kg/sc with this compound.

Example 23: Conditioned Avoidance Response

All antipsychotics show an inhibition of the conditioned "avoidance" response (CAR) at doses which do not cause catalepsy and do not cause escape deficits. Therefore the new compounds were tested for activity in this model. For conditioned avoidance-response, rats were trained and tested in a computer assisted two-way active avoidance (shuttlebox), with an 80 dB white-noise as a conditioned stimulus, followed ten seconds later by a 0.6 mA shock as the unconditioned stimulus. Details of the procedure have been described elsewhere (Wadenberg ML et al. 2000). The tests were first validated by documenting that haloperidol (> 0.05 mg/kg/sc) and clozapine (> 10 mg/kg/sc) gave rise to robust inhibition of avoidance, without catalepsy or escape deficits.

The compound of Example 6 showed > 50% inhibition of CAR at doses of 10 mg/kg/sc. The compound of example 7 showed > 50% inhibition of CAR at doses of 20 mg/kg/sc.

Example 24: FOS Immunohistochemistry

It is thought that drug-induced immediate-early-gene product FOS provides a valid marker for identifying antipsychotics that do not give rise extrapyramidal side-effects. In particular, all antipsychotics induce FOS in the nucleus accumbens regions while those likely to give rise to motor side-effects also induce FOS in the dorsolateral striatum (Robertson et al. 1994). For examining the distribution of FOS protein by the test compound, the test compound was injected into rats and two hours later, the animals were deeply anaesthetized with sodium phenobarbitol (100 mg/kg i.p.) and perfused transcardially, the brains removed and post-fixed. Immunostaining was performed on free-floating forty-micron sections with a rabbit-raised polyclonal primary anti-FOS antiserum (diluted 1:250 and incubated 48 hours at 4°C) (4-17

aminoacids of human Fos; Oncogene Research Products, Cambridge, MA, USA). Exposure to a biotinylated goat anti-rabbit secondary antibody (1:600, Vector Laboratories, Burlingame, CA, USA) followed by incubation with horseradish peroxidase - avidin-biotin complex (Vector Laboratories, Vector Laboratories, Burlingame, CA, USA) was used to visualize the FOS staining. Fos-immunoreactive nuclei were counted within 400 x 400μm grid at a magnification of 100x in the shell of nucleus accumbens and dorsolateral striatum. This procedure was validated by showing that both haloperidol and clozapine gave robust FOS induction in the nucleus accumbens, but only haloperidol resulted in FOS in the dorsolateral striatum.

In tests for FOS protein induction, the compound of Example 6 showed robust induction of FOS protein in the nucleus accumbens, with no induction of FOS protein in the dorsolateral striatum.

Index of Patents

No.	Patent No.	Issue Date	Title
1.	3,347,849	10/17/67	5-(Basic Substituted)-Dibenzodiazepines
2.	3,367,930	02/06/68	Process for the Preparation of Heterocyclic Compounds
3.	3,412,193	11/19/9/	11-(4-Methyl-1-Piperazinyl)dibenz[b,f] [1,4]Oxazepines or Thiazepines for Controlling Fertility
4.	3,444,169	05/13/69	Process for 11-Aminodibenzo[bf,][1,4] Oxazepines and Analogous Thiazepines
5.	3,539,573	11/10/70	11-Basic Substituted Dibenzodiazepines and Dibenzothiazepines
6.	3,546,226	12/08/70	11-Basic Substituted Dibenzoxazepines
7.	3,663,696	05/16/72	Treatment of Depression With 2-Chloro-11-(Piperazinyldibenz-[b,f][1,4]Oxazepines and Acid Addition Salts Thereof
8.	3,681,357	08/01/72	2-Chloro-11-(Piperazinyl)Dibenzy[b,f][1,4] Oxazepine and Acid Addition Salts Thereof
9.	5,068,437	11/26/91	Process for Producing 2-(P-Chlorophenoxy) Aniline
10.	5,393,752	02/28/95	Methylpiperazinoazepine Compounds, Preparation and Use Thereof
11.	5,602,120	02/11/97	Benzyl-Substituted Compounds Having Dopamine Receptor Affinity
12.	WO 99/31267	12/18/98	Methods for the Simultaneous Identification of Novel Biological Targets and Lead Structures for Drug Development
13.	436 297 [CH]	05/31/67	Verfahren zur Herstellung 11-Basich substituierter Dibenz[b,f]-[1,4]oxazepine
14.	1,164,360 [GB]	11/30/67	A Process for Preparing Tricyclic Organic Compounds

Index of Articles

No.	Author	Title	Citation
15.	Ahlenius, S., et al.	Involvement of Extrapyramidal Motor Mechanisms in the Suppression of Locomotor Activity by Antipsychotic Drugs: A Comparison Between the Effects Produced by Pre- and Post-Synaptic Inhibition of Dopaminergic Neurotransmission	Pharmac., Biochem. & Behavior, Vol. 24, pp. 1409-1415 (986) (Ahlenius S et al. 1986)
16.	Bartl, V., et al.	Neurotropic and Psychotropic Agents. LXV: 8-Chloro and 8-Isopropyl-6-Piperazinobenzo(*b*)Pyrido[3,2-*f*] Thiepin	Collection Czech. Chem. Community (Vol. 38), pp. 2778-2787 (1973)
17.	Bartl, V., et al.	Neurotropic and Psychotropic Agents. LXI: Derivatives of 6-Piperazinobenzo[*b*]Pyrido[3,2-*f*]Thiepin	Collection Czech. Chem. Community (Vol. 38), pp. 1693-1699 (1973)
18.	Casey, D.E.	Extrapyramidal Syndromes	CMS Drugs, 5 Supp., pp. 1-12 (1996) (Casey 1996)
19.	Farde, L., et al.	Positron Emission Tomographic Analysis of Central D_1 and D_2 Dopamine Receptor Occupancy in Patients Treated With Classical Neuroleptics and Clozapine	Arch. Gen. Psychiatry, Vol. 49, pp. 538-544 (1992) (Farde et al. 1997)
20.	Farde, L., et al.	Central D2-Dopamine Receptor Occupancy in Schizophrenic Patients Treated with Antipsychotic Drugs	Arch. Gen. Psychiatry, Vol. 45, pp. 71-76 (1988) (Farde et al. 1997)
21.	Jegouzo, A., et al.	Comparative oxidation of loxapine and clozapine by human neutrophils	Fundam. Clin. Pharmacol. Vol. 13, pp. 113-119 (1999) (Jegouzo et al. 1999)
22.	Jiler, J., et al.	Neurotrope Und Psychotrope Substanzen. XIX: 8-Halogenderivate von 10-(4-Methylpiperazino)-10,11-Dihydrodibenzo(*b,f*)Thiepin und Verwandte Substanzen	Collection Czech. Chem. Community (Vol. 33), pp. 1831-1845 (1968)
23.	Kapur, S., et al.	Does Fast Dissociation From the Dopamine D_2 Receptor Explain the Action of Atypical Antipsychotics?: A New Hypothesis	Am. J. Psychiatry, Vol. 158:3, pp. 360-369 (March 2001)
24.	Kapur, S., et al.	Antipsychotic agents differ in how fast they come of the dopamine D_2 receptors. Implications for atypical antipsychotic action	J. Psych. & Neuroscience, Vol. 25, No. 2, pp. 161-166 (2000) (Kapur and Seeman 2000a)

No.	Author	Title	Citation
25.	Kapur, S., et al.	Are Animal Studies of Antipsychotics Appropriately Dosed?: Lessons From the Bedside to the Bench	Can. J. Psychiatry, Vol. 45, pp. 241-245 (2000) (Kapur et al. 2000b)
26.	Liegeois, J.F., et al.	Pyrodibenzoxazepine and Pyridobenzothiazepine Derivatives as Potential Central Nervous System Agents: Synthesis and Neurochemical Study	J. Med. Chem. Vol. 37, pp. 519-525, 1994
27.	Moore, K.	Interactions between Prolactin and Dopaminergic Neurons	Biology of Reproduction, Vol. 36, pp. 47-58 (1987) (Moore 1987)
28.	Pelz, K., et al.	Neurotrope und Psychotrope Substanzen. XXV: Uber die in 8-Stellung Durch die Methyl-, Tert-Butyl-, Methoxy-, Methylthio-, und methansulfonylgruppe Substituierten 10-(4-Methylpiperazino)-10,11-Dihydrodibenzo[*b,f*]Thiepin-Derivate	Collection Czech. Chem. Community (Vol. 33), pp. 1895-1910 (1968)
29.	Robertson, G. et al.	Induction Patterns of Fos-Like Immunoreactivity in the Forebrain as Predictors of Atypical Antipsychotic Activity	Jnl. Pharmacol. & Exper. Therap. Vol. 271, No. 2, pp. 1058-1066, 1994 (Robertson et al. 1994)
30.	Seeman, P. et al.	Deriving the therapeutic concentrations for clozapine and haloperidol: The apparent dissociation constant of a neuroleptic at the dopamine D_2 receptor varies with the affinity of the competing radioligand	Eur. Jnl of Pharmac., Molecular Pharmac. Section 291, pp. 59-66, (1993) (Seeman 1993)
31.	Seeman, P. et al.	Antipsychotic drugs which elicit little or no Parkinsonism bind more loosely than dopamine to brain D2 receptors, yet occupy high levels of these receptors	Molecular Psych. Vol. 3, pp. 123-134, (1998) (Seeman and Tallerico 1998)
32.	Seeman, P. et al.	Rapid release of Antipsychotic Drugs From Dopamine D_2 Receptors: An Explanation for Low Receptor Occupancy and Early Clinical Relapse Upon Withdrawal of Clozapine or Quetiapine	Am. J. Psychiatry, Vol. 156, pp. 676-684 (1999)
33.	Uetrecht, J. et al.	Structural features associated with reactive metabolite formation in clozapine analogues	Chemico-Biological Interactions, Vol. 104, pp. 117-129 (1997) (Uetrecht et al. 1997)

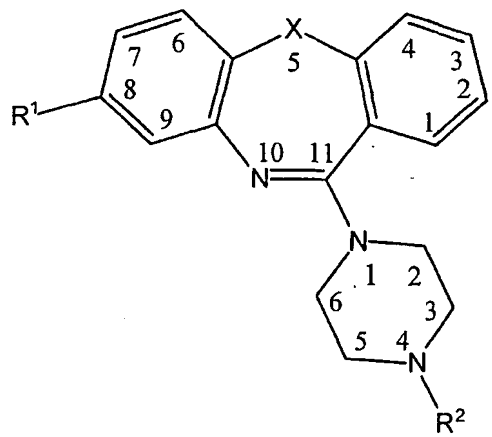
No.	Author	Title	Citation
34.	Uetrecht, J. et al.	Reactive metabolites and agranulocytosis	Eur. Jnl Haemotology, Vol. 57, pp. 83-88 (1996) (Uetrecht 1996)
35.	Wadenberg, M. et al.	Dopamine D_2 receptor occupancy predicts catalepsy and the suppression of conditioned avoidance response behavior in rats	Psychopharmacology, Vol. 150, pp. 420-429 (2000) (Wadenberg M.L. et al. 2000)

All publications, references, articles, patents and patent applications cited herein are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

While the present invention has been described with reference to what are presently considered to be the preferred examples, it is to be understood that the invention is not limited to the disclosed examples. To the contrary, the invention is intended to cover various modifications and equivalent arrangements included within the spirit and scope of the appended claims.

WHAT IS CLAIMED IS:

1. A compound of Formula I or a pharmaceutically acceptable salt, hydrate, prodrug or solvate thereof, wherein said Formula I is represented by:



I

and wherein

R^1 is selected from the group consisting of halo, CF_3, CF_3O, cyano, CH_3 and CH_3O;

R^2 is selected from the group consisting of $C_{2\text{-}5}$ alkyl and $(CH_2)_nOH$;

X is selected from the group consisting of O and S; and

n is an integer selected from 2, 3, 4 and 5.

2. The compound of claim 1, or a pharmaceutically acceptable salt, hydrate, prodrug or solvate thereof, wherein X is O.

3. The compound of claim 1, or a pharmaceutically acceptable salt, hydrate, prodrug or solvate thereof, wherein X is S.

4. The compound of claim 1, or a pharmaceutically acceptable salt, hydrate, prodrug or solvate thereof, wherein R^2 is $C_{2\text{-}4}$ alkyl.

5. The compound of claim 1, or a pharmaceutically acceptable salt, hydrate, prodrug or solvate thereof, wherein R^2 is selected from the group consisting of ethyl, n-propyl, isopropyl, n-butyl and $(CH_2)_2OH$.

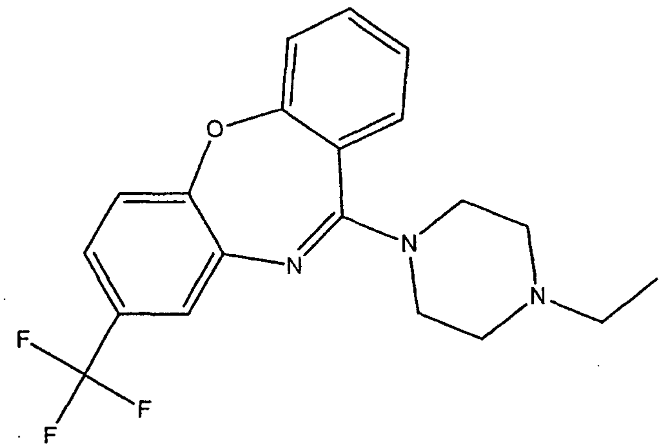
6. The compound of claim 5, or a pharmaceutically acceptable salt, hydrate, prodrug or solvate thereof, wherein R^2 is selected from the group consisting of ethyl and $(CH_2)_2OH$.

7. The compound of claim 6, or a pharmaceutically acceptable salt, hydrate, prodrug or solvate thereof, wherein R^1 is selected from the group consisting of halo and CF_3.

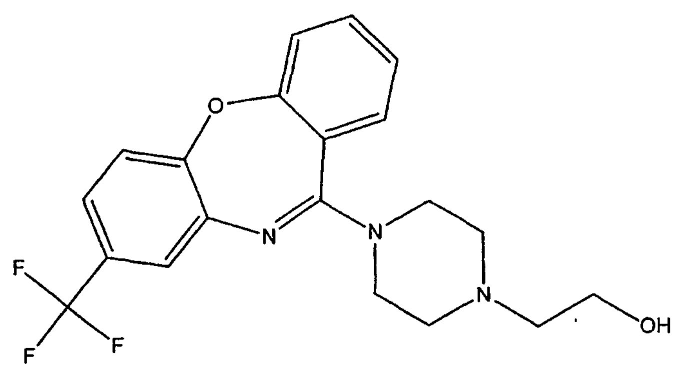
8. The compound of claim 7, or a pharmaceutically acceptable salt, hydrate, prodrug or solvate thereof, wherein R^1 is selected from the group consisting of F, Cl, Br and I.

9. The compound of claim 7, or a pharmaceutically acceptable salt, hydrate, prodrug or solvate thereof, wherein R^1 is selected from the group consisting of Cl and CF_3.

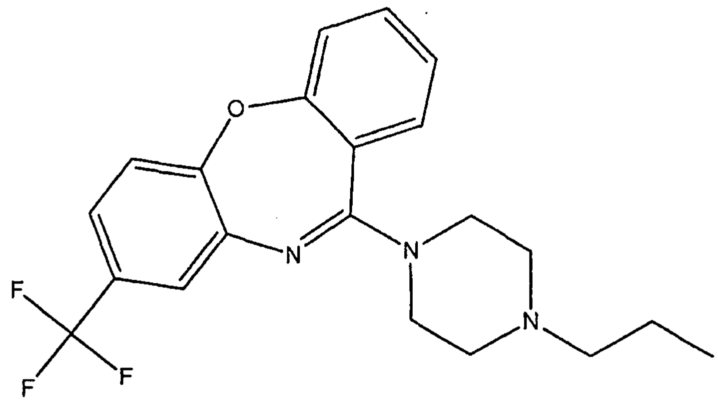
10. The compound of claim 1, wherein said compound of Formula (I) is selected from the group consisting of:



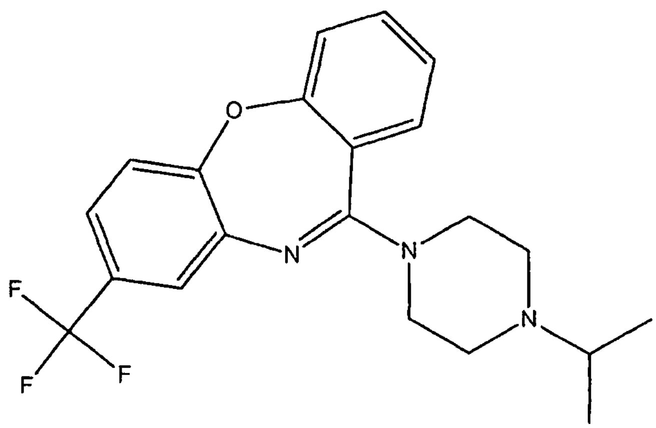
(A-1) = 8-Trifluoromethyl-11-(4-ethylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;



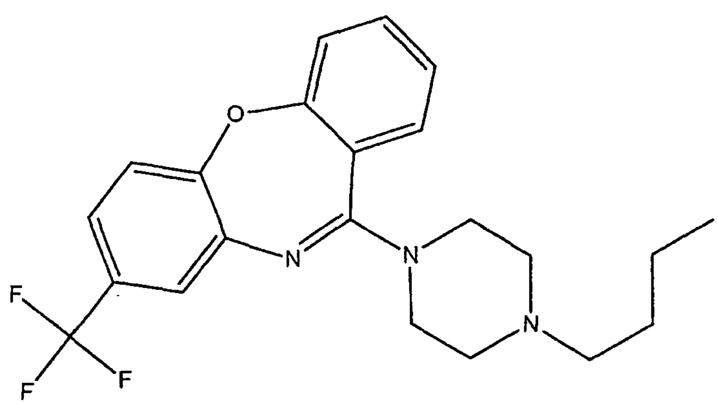
(A-2) = 8-Trifluoromethyl-11-(4-(2'-hydroxyethyl)piperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;



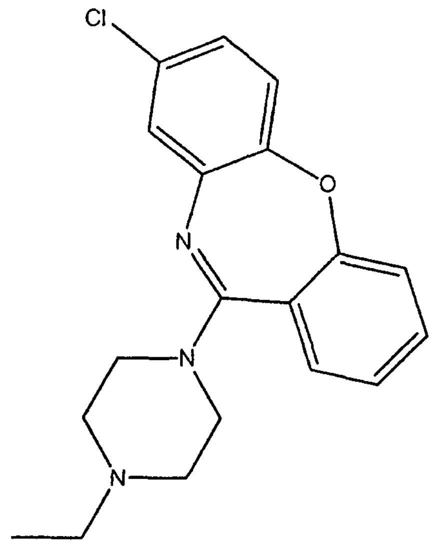
(A-3) = 8-Trifluoromethyl-11-(4-propylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;



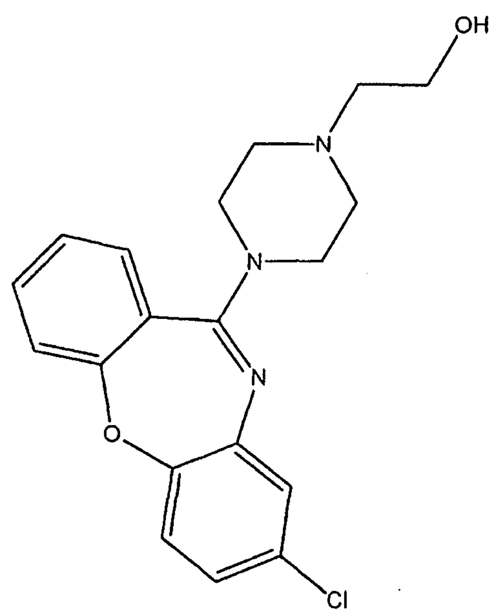
(A-4) = 8-Trifluoromethyl-11-(4-isopropylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;



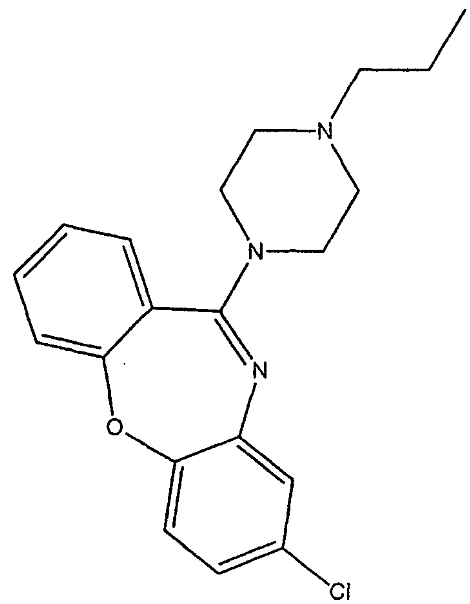
(A-5) = 8-Trifluoromethyl-11-(4-butylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;



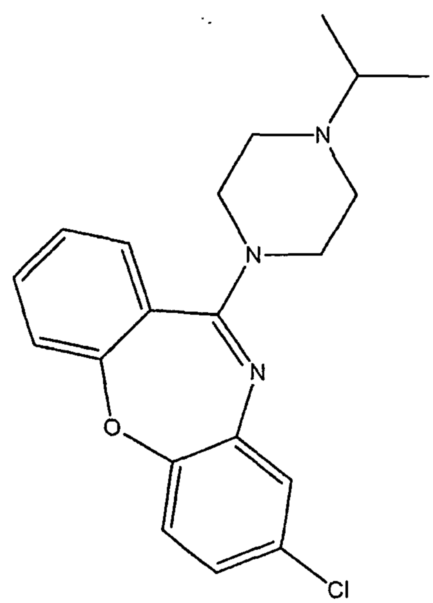
(A-6) = 8-Chloro-11-(4-ethylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;



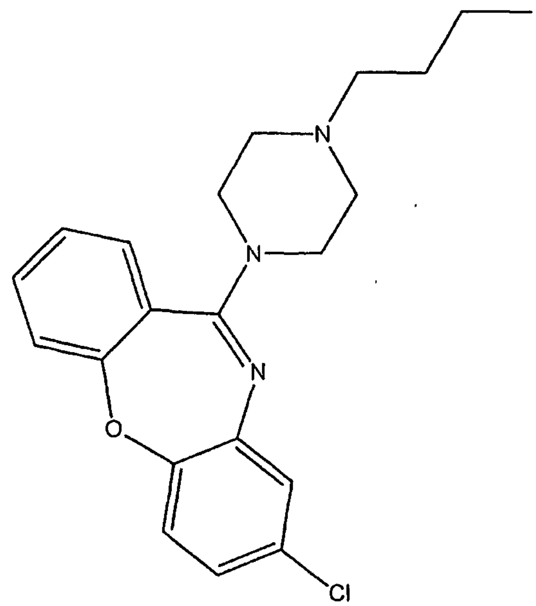
(A-7) = 8-Chloro-11-(4-(2'-hydroxyethyl)piperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;



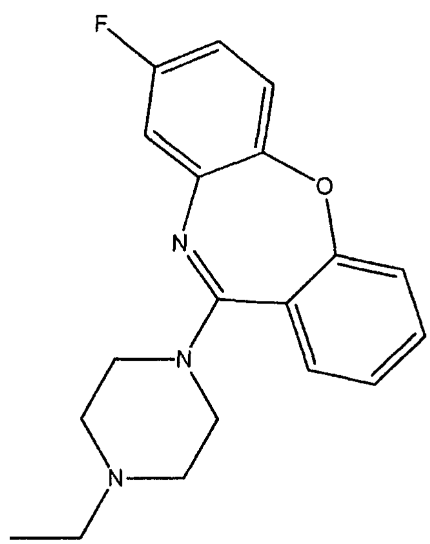
(A-8) = 8-Chloro-11-(4-propylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;



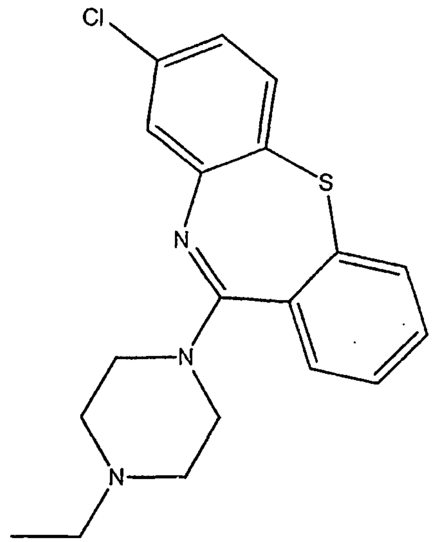
(A-9) = 8-Chloro-11-(4-isopropylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;



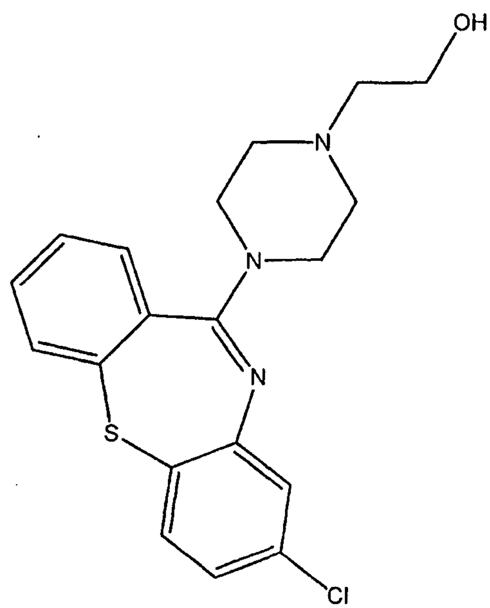
(A-10) = 8-Chloro-11-(4-butylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;



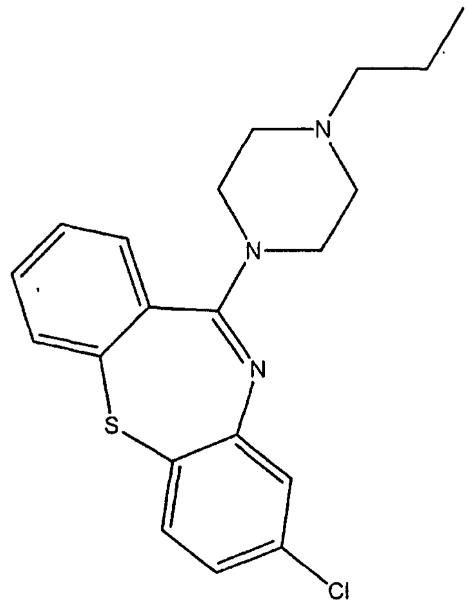
(A-11) = 8-Fluoro-11-(4-ethylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;



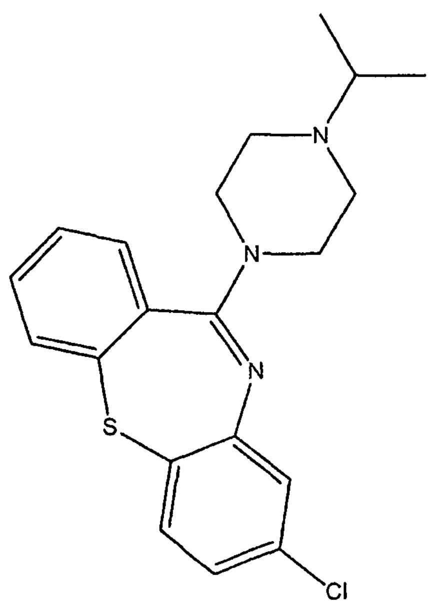
(A-12) = 8-Chloro-11-(4-ethylpiperazin-1-yl)-dibenzo [b,f][1,4]thiazepine;



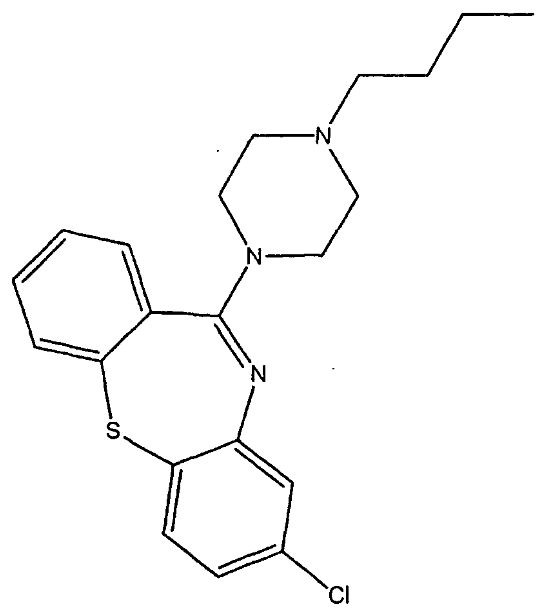
(A-13) = 8-Chloro-11-(4-(2'-hydroxyethyl)piperazin-1-yl)-dibenzo[b,f][1,4]thiazepine;



(A-14) = 8-Chloro-11-(4-propylpiperazin-1-yl)-dibenzo[b,f][1,4]thiazepine;



(A-15) = 8-Chloro-11-(4-isopropylpiperazin-1-yl)-dibenzo[b,f][1,4]thiazepine; and



(A-16) = 8-Chloro-11-(4-butylpiperazin-1-yl)-dibenzo[b,f][1,4]thiazepine.

11. The compound of claim 1, or a pharmaceutically acceptable salt, hydrate, prodrug or solvate thereof, wherein said compound has a K_i value of at least 30nM.

12. The compound of claim 1, or a pharmaceutically acceptable salt, hydrate, prodrug or solvate thereof, wherein said compound has a K_i value from 30nM to about 500nM.

13. The compound of claim 1, or a pharmaceutically acceptable salt, hydrate, prodrug or solvate thereof, wherein said compound has a K_i value of at least about 40nM.

14. The compound of claim 1, or a pharmaceutically acceptable salt, hydrate, prodrug or solvate thereof, wherein said compound has a K_i value from about 40nM to about 500nM.

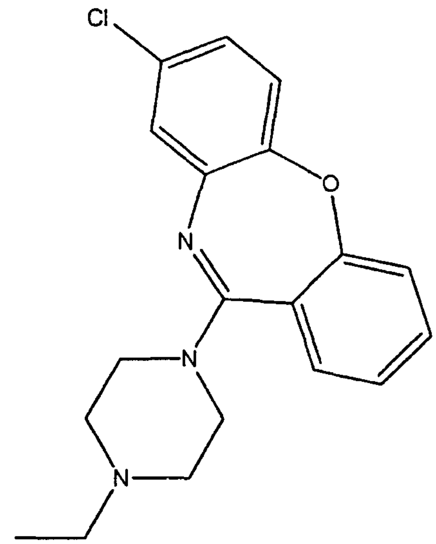
15. The compound of claim 1, or a pharmaceutically acceptable salt, hydrate, prodrug or solvate thereof, wherein said compound has a K_i value from about 40nM to about 180nM.

16. The compound of claim 1, or a pharmaceutically acceptable salt, hydrate, prodrug or solvate thereof, wherein said compound has a K_i value from about 40nM to about 80nM.

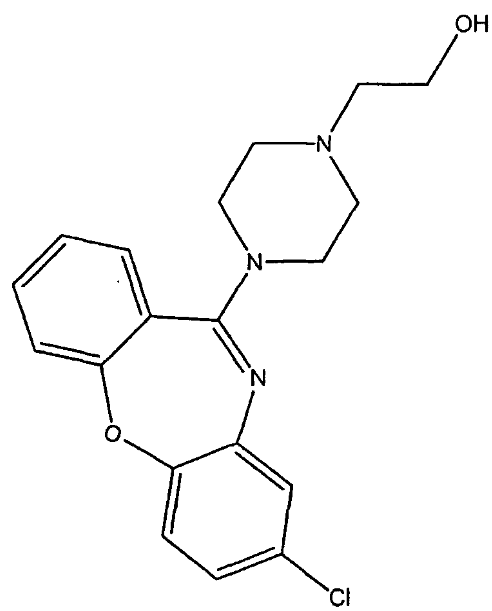
17. The compound of claim 1, or a pharmaceutically acceptable salt, hydrate, prodrug or solvate thereof, wherein said compound has a K_i value of at least about ½ times (K_i for clozapine).

18. The compound of claim 1, or a pharmaceutically acceptable salt, hydrate, prodrug or solvate thereof, wherein said compound has a K_i value from about ½ times (K_i for clozapine) to about 2 times (K_i for clozapine).

19. The compound of claim 1, or a pharmaceutically acceptable salt, hydrate, prodrug or solvate thereof, wherein said compound is selected from the group consisting of:



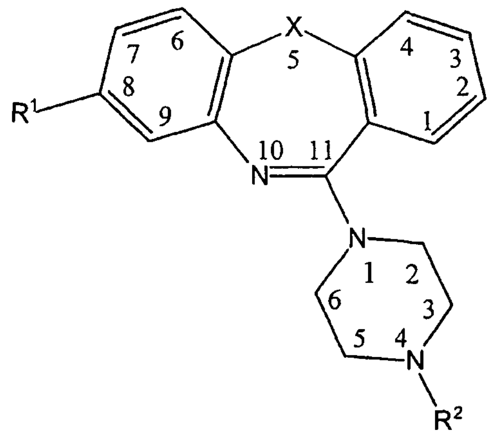
(A-6) = 8-Chloro-11-(4-ethylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine; and



(A-7) = 8-Chloro-11-(4-(2'-hydroxyethyl)piperazin-1-yl)-dibenzo[b,f][1,4]oxazepine.

20. A method for the treatment of psychosis, said method comprising the step of administering, to a subject in need thereof, a therapeutically effective amount

of a compound, or a pharmaceutically acceptable salt, hydrate, prodrug or solvate thereof, of Formula I:



I

wherein:

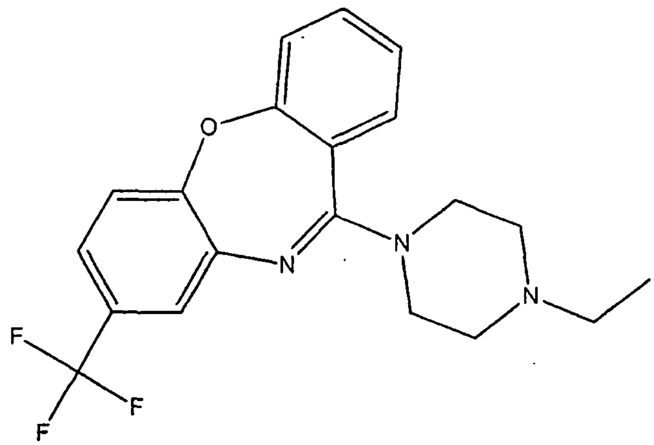
R^1 is selected from the group consisting of halo, CF_3, CF_3O, cyano, CH_3 and CH_3O;

R^2 is selected from the group consisting of $C_{2\text{-}5}$ alkyl and $(CH_2)_nOH$;

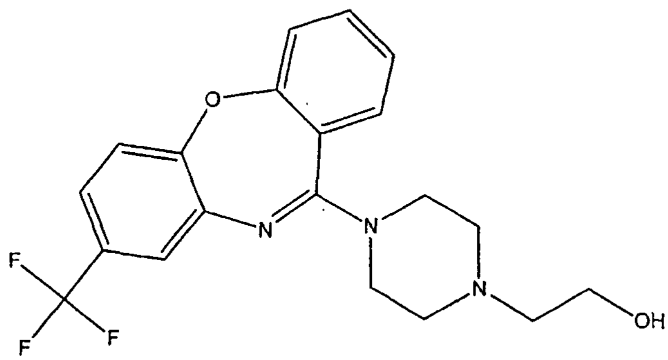
X is selected from the group consisting of O and S; and

n is an integer selected from 2, 3, 4, and 5.

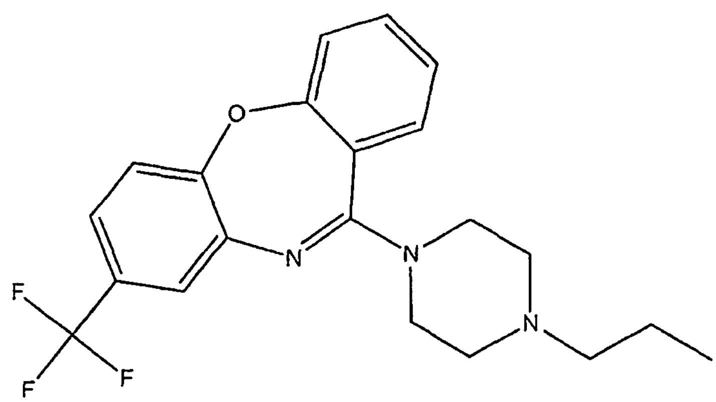
21. The method of claim 20, wherein said compound, or a pharmaceutically acceptable salt, hydrate, prodrug or solvate thereof, of Formula I is selected from the group consisting of:



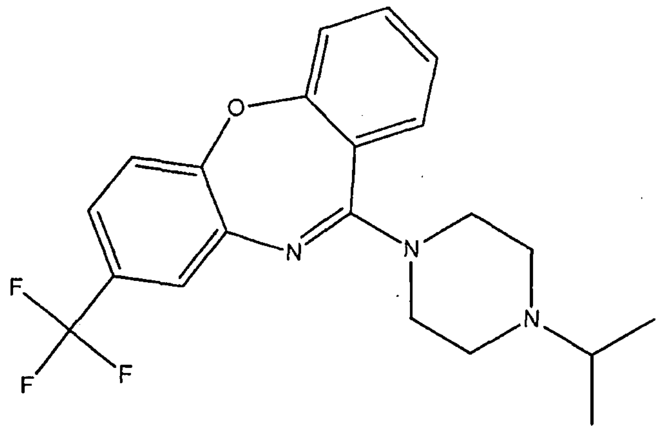
(A-1) = 8-Trifluoromethyl-11-(4-ethylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;



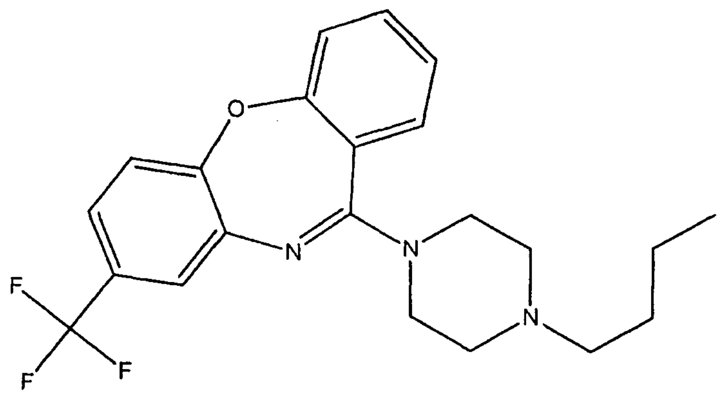
(A-2) = 8-Trifluoromethyl-11-(4-(2'-hydroxyethyl)piperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;



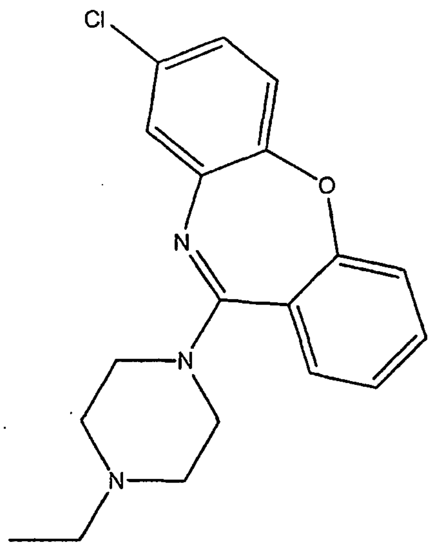
(A-3) = 8-Trifluoromethyl-11-(4-propylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;



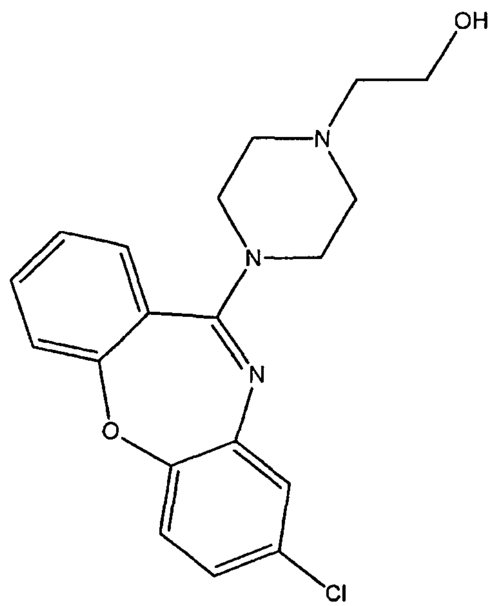
(A-4) = 8-Trifluoromethyl-11-(4-isopropylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;



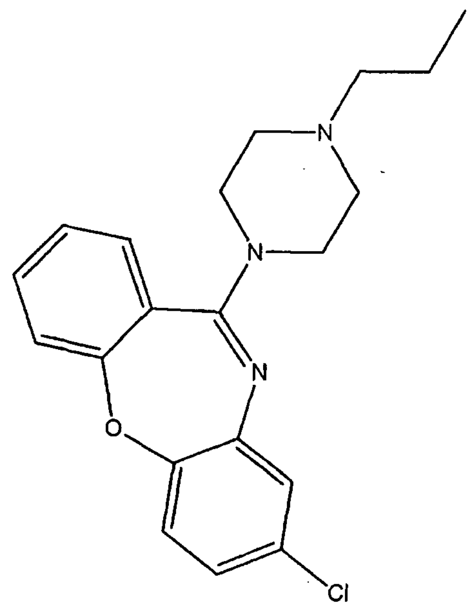
(A-5) = 8-Trifluoromethyl-11-(4-butylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;



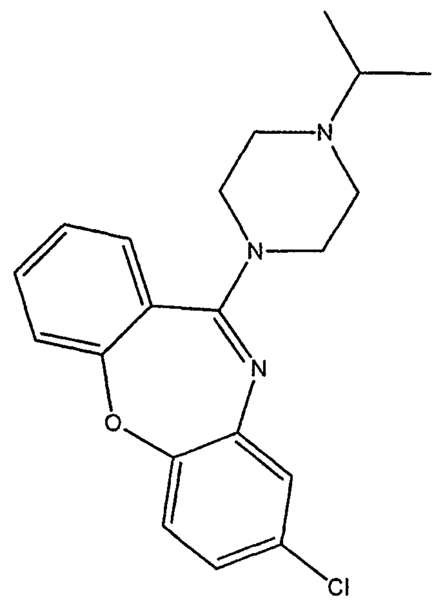
(A-6) = 8-Chloro-11-(4-ethylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;



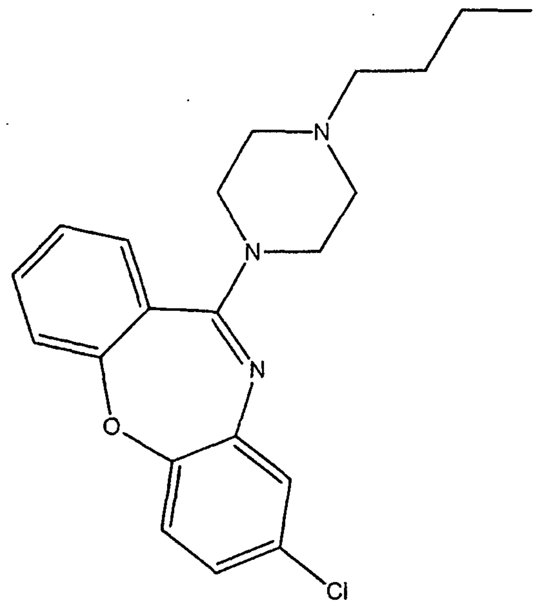
(A-7) = 8-Chloro-11-(4-(2'-hydroxyethyl)piperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;



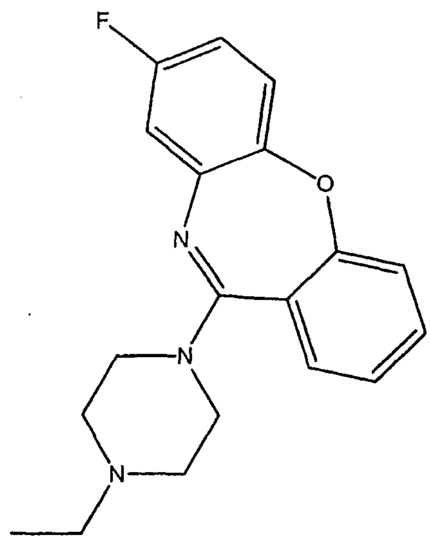
(A-8) = 8-Chloro-11-(4-propylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;



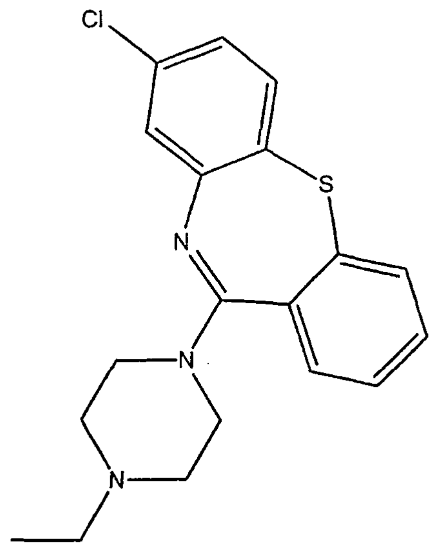
(A-9) = 8-Chloro-11-(4-isopropylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;



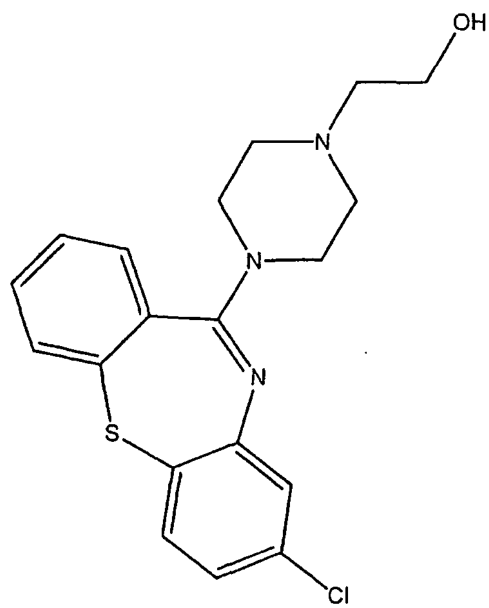
(A-10) = 8-Chloro-11-(4-butylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;



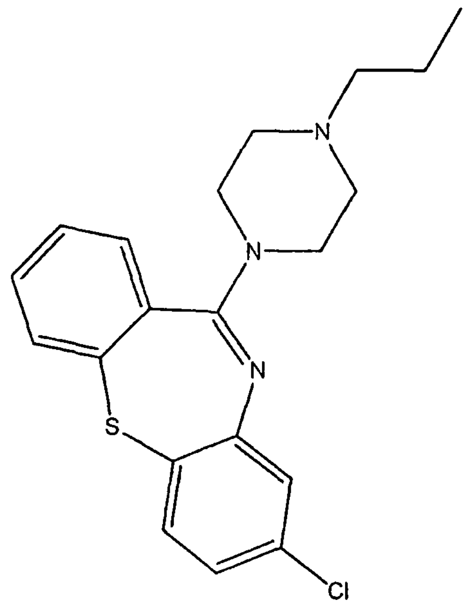
(A-11) = 8-Fluoro-11-(4-ethylpiperazin-1-yl)-dibenzo[b,f][1,4]oxazepine;



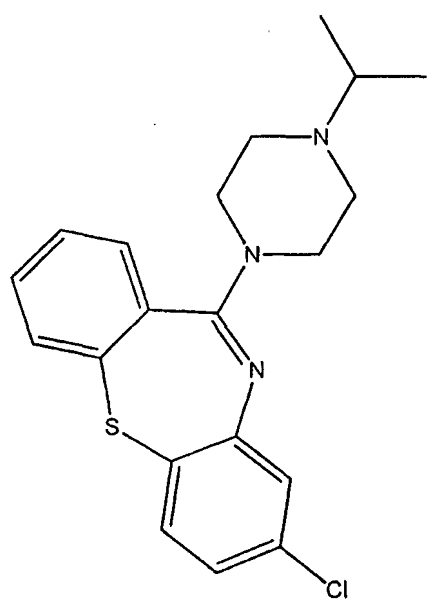
(A-12) = 8-Chloro-11-(4-ethylpiperazin-1-yl)-dibenzo [b,f][1,4]thiazepine;



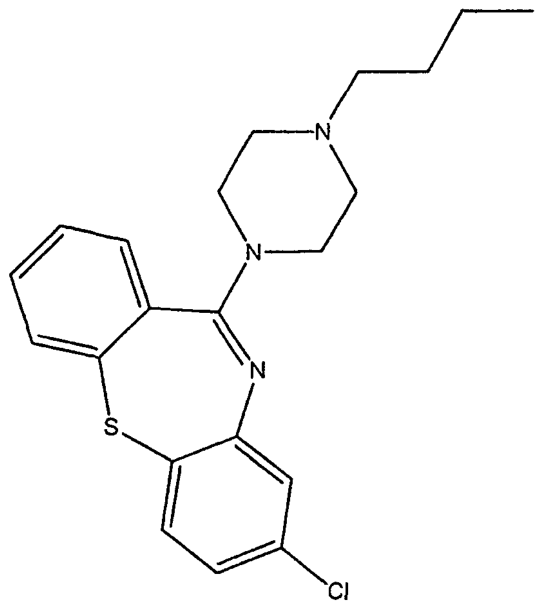
(A-13) = 8-Chloro-11-(4-(2'-hydroxyethyl)piperazin-1-yl)-dibenzo[b,f][1,4]thiazepine;



(A-14) = 8-Chloro-11-(4-propylpiperazin-1-yl)-dibenzo[b,f][1,4]thiazepine;

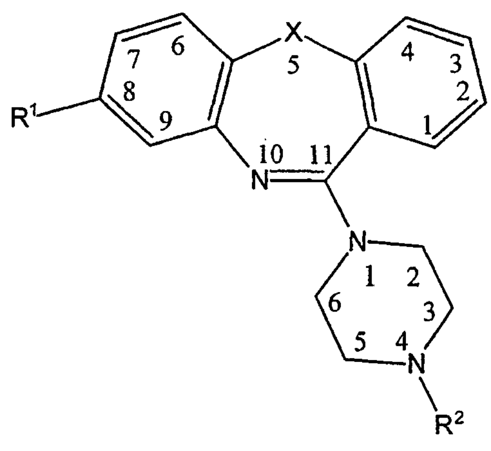


(A-15) = 8-Chloro-11-(4-isopropylpiperazin-1-yl)-dibenzo[b,f][1,4]thiazepine; and



(A-16) = 8-Chloro-11-(4-butylpiperazin-1-yl)-dibenzo[b,f][1,4]thiazepine.

22. A pharmaceutical composition comprising a compound of Formula I, or its pharmaceutical salt, hydrate or solvate thereof, and a pharmaceutically acceptable carrier, said Formula I represented by:



I

wherein:

R^1 is selected from the group consisting of halo, CF_3, CF_3O, cyano, CH_3 and CH_3O;

R^2 is selected from the group consisting of C_{2-5} alkyl and $(CH_2)_nOH$;

X is selected from the group consisting of O and S; and

n is an integer selected from 2, 3, 4, and 5.

23. The method of claim 20, wherein said administering step comprises orally administering, for the treatment of schizophrenia, said compound, or a pharmaceutically acceptable salt, hydrate, prodrug or solvate thereof, of Formula I.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 02/00956

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D267/20 C07D281/16 A61K31/553 A61K31/554 A61P25/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CH 422 793 A (WANDER AG DR A) 31 October 1966 (1966-10-31) Claim 1; examples 16-18,20,27,42. ---	1-23
A	US 3 539 573 A (HUNZIKER FRITZ ET AL) 10 November 1970 (1970-11-10) cited in the application Claim 1; examples. ---	1-23
A	CH 450 426 A (WANDER AG DR A) 31 January 1968 (1968-01-31) Claim 1; examples 3,23. ---	1-23
A	US 3 546 226 A (HUNZIKER FRITZ ET AL) 8 December 1970 (1970-12-08) cited in the application Columns 1-2; claim 1, example 2. --- -/--	1-23

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 September 2002	30/09/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Weisbrod, T

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 02/00956

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 01164 A (RESOLUTION PHARM INC) 15 January 1998 (1998-01-15) Claims 1-20; examples.	1-23
X	US 5 834 459 A (FU JIAN-MIN) 10 November 1998 (1998-11-10) Column 2, lines 1-31; column 4, lines 47-49 and 59-61.	1-23
X	WARAWA, E. J. ET AL.: "Behavioral approach to nondyskinetic dopamine antagonists: Identification of Seroquel" J. MED. CHEM., vol. 44, 1 February 2001 (2001-02-01), pages 372-389, XP002213291 Compounds 7,8,28.	1-23

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-9,11-21,23 (all part)

the scope of the claims 1-9, 11-21 and 23, in as far as the expression prodrug is concerned, is so unclear (Article 6 PCT) that a meaningful International search is impossible with regard to this expression. Nevertheless the search was complete for esters of hydroxy compounds (I).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/CA 02/00956

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

   Although claims 20, 21 and 23 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-9,11-21,23 (all part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

   see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 02/00956

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
CH 422793	A	31-10-1966	NONE			
US 3539573	A	10-11-1970	CH	481133	A	15-11-1969
			CH	485752	A	15-02-1970
			AT	292716	B	15-08-1971
			AT	292717	B	15-08-1971
			AT	292718	B	15-08-1971
			AT	292707	B	15-08-1971
			BE	712114	A	13-09-1968
			CH	517759	A	15-01-1972
			CH	514612	A	31-10-1971
			CH	499539	A	30-11-1970
			CH	481940	A	30-11-1969
			CH	481941	A	30-11-1969
			CH	481942	A	30-11-1969
			DE	1720007	A1	19-05-1971
			ES	351389	A1	01-12-1969
			FR	8046	M	10-08-1970
			GB	1216523	A	23-12-1970
			IL	29571	A	27-04-1972
			NL	6406089	A	01-12-1964
			NL	6803570	A	16-09-1968
			NO	123459	B	22-11-1971
			SE	364277	B	18-02-1974
			US	3852446	A	03-12-1974
			US	3546226	A	08-12-1970
			US	3683034	A	08-08-1972
			US	3751415	A	07-08-1973
			US	3758479	A	11-09-1973
			US	3793325	A	19-02-1974
			US	3908010	A	23-09-1975
			AT	292719	B	15-08-1971
			AT	292722	B	15-08-1971
			CH	485765	A	15-02-1970
			CH	485748	A	15-02-1970
			CH	485749	A	15-02-1970
			CH	485750	A	15-02-1970
			AT	292720	B	15-08-1971
			AT	292721	B	15-08-1971
			US	3884920	A	20-05-1975
CH 450426	A	31-01-1968	CH	436297	A	31-05-1967
			CH	450422	A	31-01-1968
			US	3158623	A	24-11-1964
			BE	648683	A	01-12-1964
			CH	450424	A	31-01-1968
			CH	450425	A	31-01-1968
			DE	1470426	A1	18-12-1969
			DK	118463	B	24-08-1970
			FI	42214	B	02-03-1970
			FR	3485	M	
			FR	3488	M	
			GB	1045903	A	19-10-1966
			NL	6406089	A	01-12-1964
			NL	140242	B	15-11-1973
			NO	115657	B	11-11-1968
			SE	317382	B	17-11-1969
			SE	300111	B	08-04-1968

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 02/00956

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CH 450426 A		US 3546226 A	08-12-1970
		US 3683034 A	08-08-1972
		FR 1386724 A	22-01-1965
		GB 1034195 A	29-06-1966
US 3546226 A	08-12-1970	CH 481133 A	15-11-1969
		CH 484924 A	31-01-1970
		CH 436297 A	31-05-1967
		CH 450422 A	31-01-1968
		US 3158623 A	24-11-1964
		AT 292716 B	15-08-1971
		AT 292717 B	15-08-1971
		AT 292718 B	15-08-1971
		AT 292707 B	15-08-1971
		BE 712114 A	13-09-1968
		CH 517759 A	15-01-1972
		CH 514612 A	31-10-1971
		CH 499539 A	30-11-1970
		DE 1720007 A1	19-05-1971
		ES 351389 A1	01-12-1969
		FR 8046 M	10-08-1970
		GB 1216523 A	23-12-1970
		IL 29571 A	27-04-1972
		NL 6406089 A	01-12-1964
		NL 6803570 A	16-09-1968
		NO 123459 B	22-11-1971
		SE 364277 B	18-02-1974
		US 3852446 A	03-12-1974
		US 3683034 A	08-08-1972
		CH 481940 A	30-11-1969
		CH 481941 A	30-11-1969
		CH 481942 A	30-11-1969
		US 3539573 A	10-11-1970
		US 3751415 A	07-08-1973
		US 3758479 A	11-09-1973
		US 3793325 A	19-02-1974
		US 3908010 A	23-09-1975
		CH 484937 A	31-01-1970
		CH 484926 A	31-01-1970
		CH 484927 A	31-01-1970
		CH 484928 A	31-01-1970
		BE 648683 A	01-12-1964
		CH 450424 A	31-01-1968
		CH 450425 A	31-01-1968
		CH 450426 A	31-01-1968
		DE 1470426 A1	18-12-1969
		DK 118463 B	24-08-1970
		FI 42214 B	02-03-1970
		FR 3485 M	
		FR 3488 M	
		GB 1045903 A	19-10-1966
		NL 140242 B	15-11-1973
		NO 115657 B	11-11-1968
		SE 317382 B	17-11-1969
		SE 300111 B	08-04-1968
WO 9801164 A	15-01-1998	AU 3250997 A	02-02-1998
		WO 9801164 A1	15-01-1998

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 02/00956

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5834459 A	10-11-1998	US 5602121 A	11-02-1997
		AU 3934595 A	03-07-1996
		CA 2207771 A1	20-06-1996
		WO 9618621 A1	20-06-1996